Fourth International Congress on Diseases of the Chest
Cologne, Germany — August 19-23, 1956

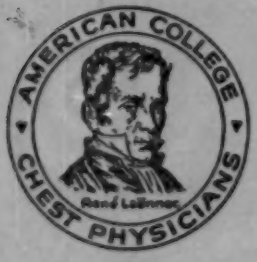
VOLUME XXIX NUMBER 6

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

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The Use of the Systemic Hemostat Carbazochrome Salicylate

J. C. Bacala, M.D.

(Abstracted from the Western Journal of Surgery, Obstetrics, and Gynecology, 64:88 (1956)

The author emphasizes the need for dependable chemical control of bleeding and oozing, and reviews the methods that have been tried to attain hemostasis, including the use of vitamin K and bioflavonoids.

He gives the history of carbazochrome salicylate and describes the clinical work completed to demonstrate its effectiveness. It appears to be specific for conditions characterized by increased capillary permeability. It has no effect on large blood vessels; it does not alter blood components; it does not affect blood pressure or cardiac rate. It has neither vasoconstrictor or vasodilator action. The drug has no known contraindications.

He reviews 1051 cases from the files of St. Anthony Hospital, Louisville, Kentucky, of which 330 were treated with Adrenosem Salicylate. 317 were surgical cases and 13 obstetric-gynecological conditions. The treatment was given for symptomatic relief, and as a clinical recourse for patient safety.

In 1015 tonsillectomy patients the following results were noted: There was bleeding in 85 (19.8%) of 429 patients who received no medication. Patients who received a compound of oxalic and malonic acids numbered 115. Of these 16 (14%), developed bleeding. Of 248 patients receiving vitamin K preparations, 47 (19%) had postoperative hemorrhage. 233 patients received Adrenosem Salicylate. Of this group, only 16 (7%) had bleeding.

In other surgical conditions, Adrenosem was used successfully in gastrointestinal bleeding, cataract extraction, incisional seepage, and transurethral prostatectomy. It was also effective in 12 cases of epistaxis.

In the field of obstetrics and gynecology, Adrenosem controlled bleeding in menometrorrhagia, hymeneal laceration, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and in two cases of surgery during pregnancy.

The author points out that in pregnancy, seepage bleeding occurs more because of capillary permeability, and in spite of increased coagulability. Here, Adrenosem becomes specific for strengthening capillary resistance.

Many of the observations in this study, however, involved bleeding incident to trauma of incision, retraction, dissection, tearing and stretching. In these conditions, he reasons that Adrenosem causes hemostasis by its effect on the capillary intercellular cement substance so that the cells draw closer together, and the ends of the capillaries constrict, causing a "self-clamping" mechanism.

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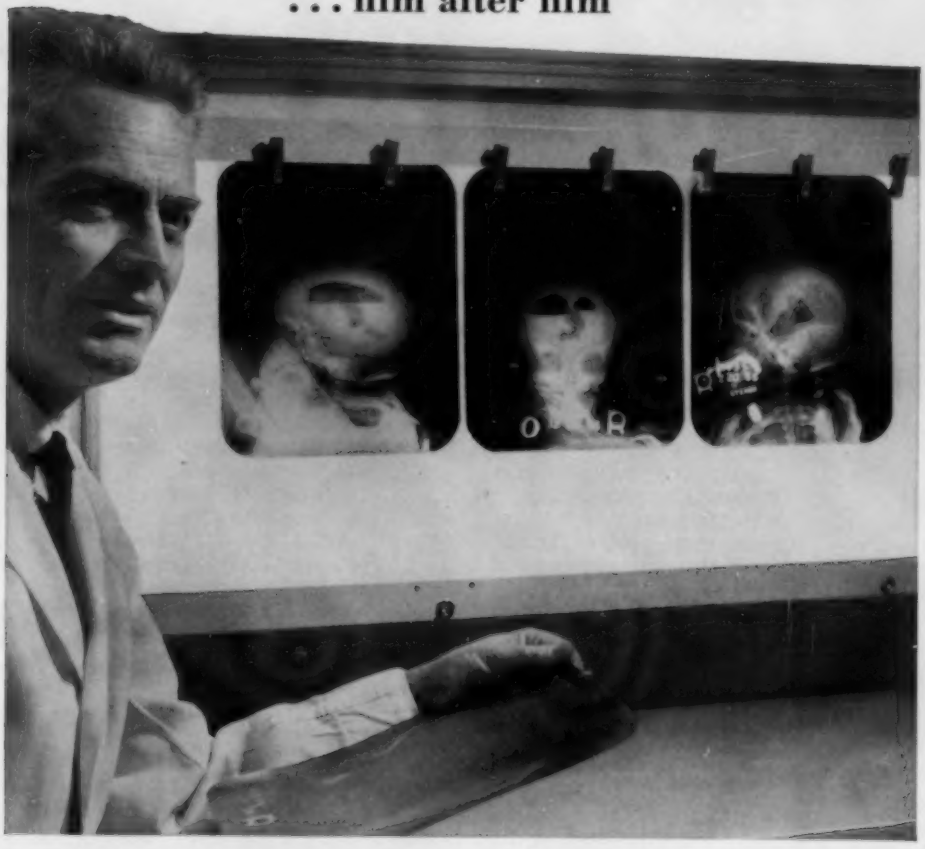

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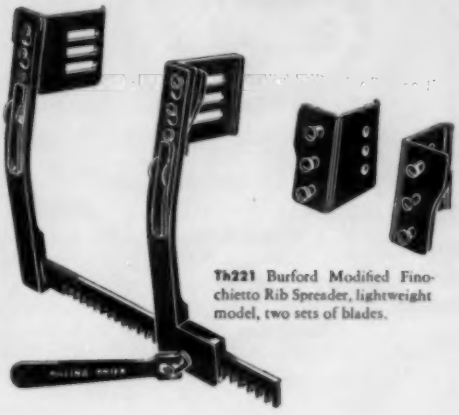

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CONTENTS

SURGERY FOR PULMONARY CANCER—A DECLARATION OF DIVIDENDS 595
Richard H. Overholt, M.D., and James A. Bougas, Boston, Massachusetts

INDICATIONS FOR COMMISSUROTOMY IN MITRAL STENOSIS 605
George C. Griffith, M.D., Los Angeles, California

INTERMITTENT POSITIVE PRESSURE-AEROSOL THERAPY IN PEDIATRICS 616
Roy F. Goddard, M.D., and Ulrich C. Luft, M.D., Albuquerque, New Mex.

ABNORMAL VENTILATORY PATTERNS IN MITRAL STENOSIS 633
R. S. Cosby, M.D., E. C. Stowell, Jr., Ph.D., W. R. Hartwig, B.S. and M. Mayo, A.B., Los Angeles, California

THE REHABILITATION TEAM IN A TUBERCULOSIS HOSPITAL: PSYCHOSOMATIC ASPECTS 641
Aaron Paley, M.D., Pearl H. Berman, M.S.S., Mary Ann Hopkins, M.S.W., and Sidney H. Dressler, M.D., Denver, Colorado

GEOGRAPHIC VARIATION IN THE PREVALENCE OF HISTOPLASMIN SENSITIVITY 649
Nicholas E. Manos, Shirley H. Ferebee and Winifred F. Kerschbaum, Washington, D. C.

THE PROGNOSIS OF BILATERAL SYMMETRICAL DIFFUSE NODULAR PULMONARY TUBERCULOSIS AND ITS POSSIBLE RELATIONSHIP TO INTESTINAL TUBERCULOSIS 669
Roger S. Mitchell, M.D., Denver, Colorado

LIVER BIOPSY IN A TUBERCULOSIS HOSPITAL 675
William H. Buckingham, M.D., George C. Turner, M.D., William B. Knapp, M.D., Quentin D. Young, M.D., and Fenton Schaffner, M.D., Oak Forest, Illinois

EDITORIAL—THE FIRST LINE OF DEFENSE IN TUBERCULOSIS: THE PRACTICING PHYSICIAN 684
Harold G. Trimble, M.D., Oakland, California

TEACHING OF CHEST RADIOLOGY TO MEDICAL STUDENTS 691
Charles T. Dotter, M.D., Portland, Oregon

FOURTH INTERNATIONAL CONGRESS 693

DR. HERMAN J. MOERSCH TAKES OFFICE AS COLLEGE PRESIDENT 695

COLLEGE NEWS 696

BOOK REVIEWS 699

OBITUARIES: Cletus J. Golinvaux 701
William J. Tewksbury 701

ANNOUNCEMENTS; CALENDAR OF EVENTS 702

AUTHOR INDEX—January-June, 1956 703

SUBJECT INDEX—January-June, 1956 707

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- long action, usually requires only two oral doses per day
- rapid absorption — promptly reduces systolic and diastolic pressures
- consistent and predictable response — smoother control
- lower dosage required than with other ganglionic blockers
- minimal likelihood of drug tolerance

Clinical observations

In a study of four ganglionic blocking agents, Winsor[1] found that the "most effective agent was SU3088 [Ecolid]...." In another comparative study, Grimson[2] reported: "Results with Ecolid have been definitely more encouraging than those with pentolinium." Patients maintained on Ecolid state that they prefer this ganglionic blocking agent because of greater energy, improved appetite, less difficulty with constipation and fewer tablets to take.[2,3]

For complete information about Ecolid, particularly more details on dosage recommendations, management of undesired effects and precautions, contact your CIBA representative or write to Medical Service Division for booklet entitled "Ecolid — A New Ganglionic Blocker for Hypertension."

References:

1. Winsor, T.: Am. J. M. Sc. *230*:133 (Aug.) 1955. 2. Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. 3. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation *11*:733 (May) 1955. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Angiology *6*:507 (Dec.) 1955. 5. Strawn, J. R., and Moyer, J. H.: Personal communication, 1955. 6. Maxwell, R. D. H., and Howie, T. J. G.: Brit. M. J. *2*:1189 (Nov. 12) 1955.

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DOSAGE: Dosage must be adjusted to the individual patient. Below is a typical plan by which treatment may be initiated.

Ambulatory patients		
DAY	A.M.	P.M.
1	25 mg.	—
2	25 mg.	25 mg.
3	50 mg.	25 mg.
4	50 mg.	50 mg.
5	75 mg.	50 mg.
6	75 mg.	75 mg.
7	100 mg.	75 mg.
8	100 mg.	100 mg.

Hospitalized patients		
DAY	A.M.	P.M.
1	50 mg.	—
2	50 mg.	50 mg.
3	100 mg.	50 mg.
4	100 mg.	100 mg.

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Number of Patients	Initial Oral Dosage	Responses	Duration of Action	References
59 (Total Series)	75 to 300 mg. daily	Compared with other ganglionic blockers, small doses of Ecolid were employed and greater hypotensive effect was obtained. Rapid absorption and long duration of hypotensive action.	Postural hypotension lasted 13.4 hours in 5 "test" patients receiving doses of 150 mg.	1
20	50 to 200 mg. daily	Blood pressure in 20 well controlled; reductions lasted twice as long as those induced by pentolinium. Each of 10 patients with previous experience with hexamethonium preferred Ecolid. Less difficulty with constipation; appetite improved; greater energy.	**	2
18	50 to 100 mg. daily	Hypertension in 18 well controlled. Supine blood pressure reduced without tachycardia. Constipation occurred infrequently.	Supine blood pressure lowered for 12 hours or more with single oral doses of 50 to 100 mg.	3,4
44	50 mg. daily	35 responded well; 14 of these became normotensive. All patients received reserpine as base therapy.	**	5
12	25 to 200 mg. daily	Blood pressure of all 12 satisfactorily controlled. Systolic blood pressure lowered average of 76 mm. Diastolic blood pressure lowered average of 42 mm.	**	6

*To date, a total of 63 investigators have reported on the use of Ecolid in more than 500 patients. They were practically unanimous in the opinion that Ecolid was highly effective. Nearly all commented on the prolonged duration of action—about 8 to 12 hours—which permitted a twice daily dosage schedule in most cases.

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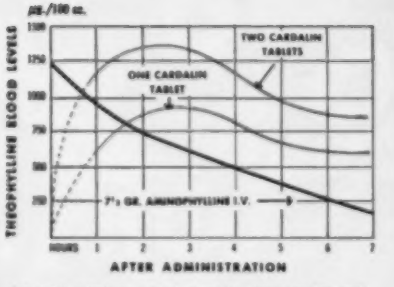

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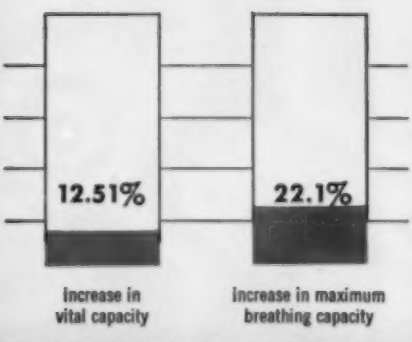

5. Cardalin works by producing high, sustained theophylline blood levels within an hour,

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2 After severe symptoms are relieved (2nd or 3rd day) reduce the dose of prednisone* to 10 mg. q.i.d.; continue Cardalin dosage.

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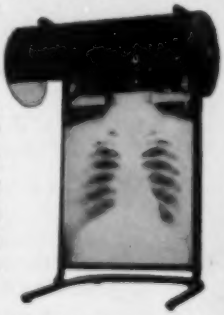

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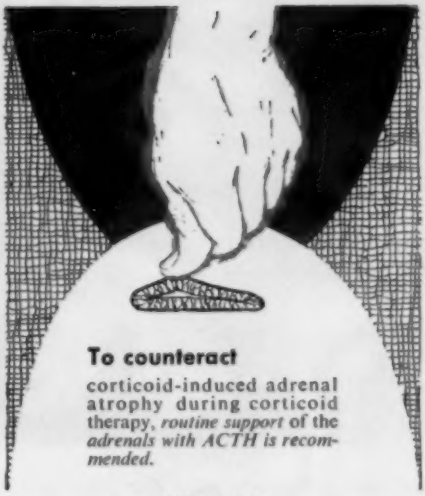

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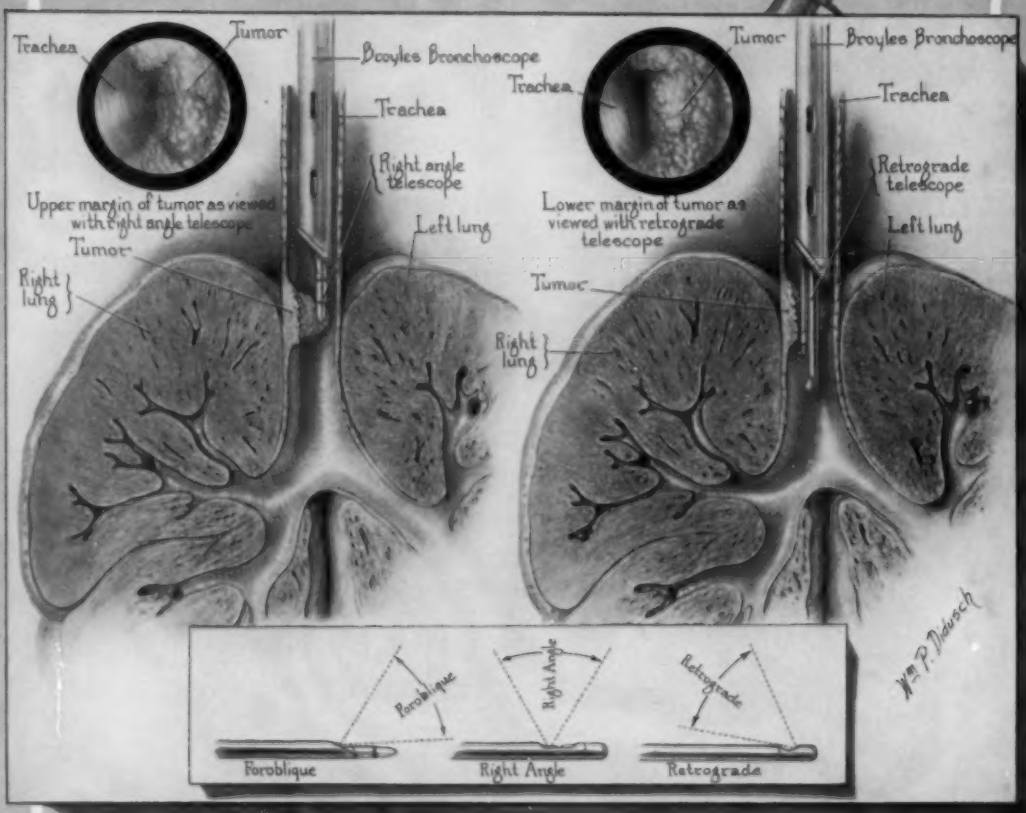

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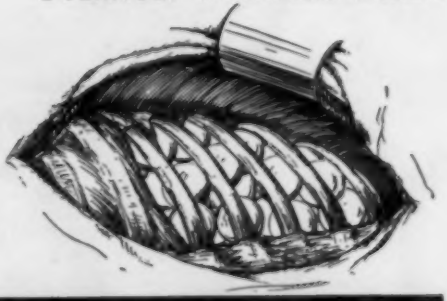

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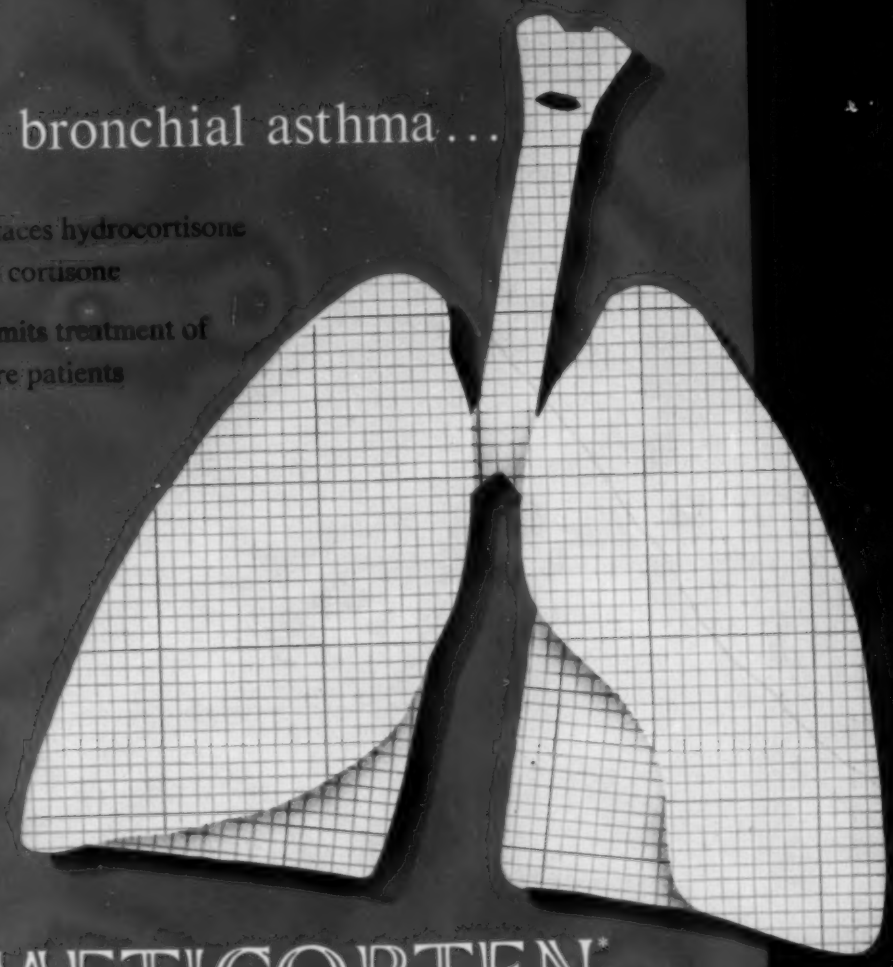

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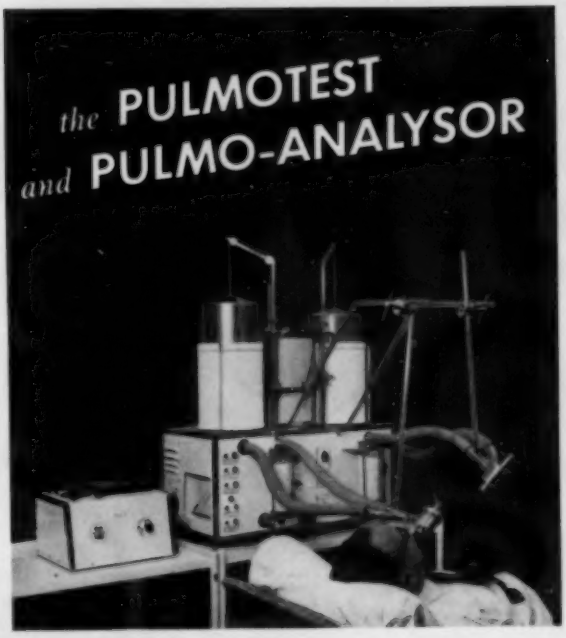

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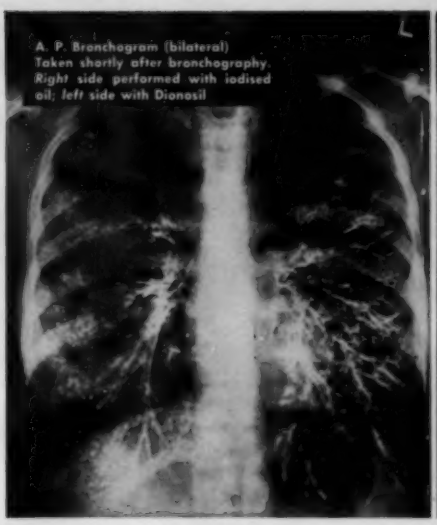
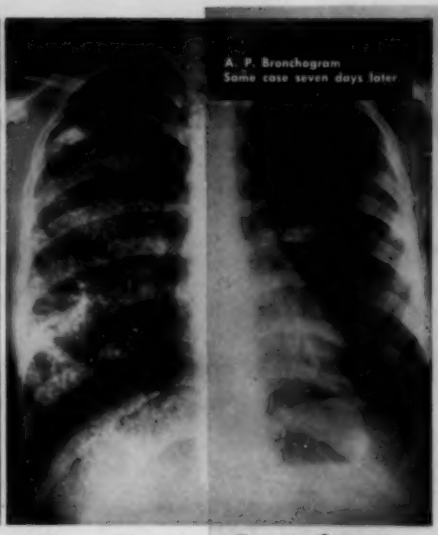


A. P. Bronchogram (bilateral)
Taken shortly after bronchography.
Right side performed with iodised oil; *left* side with Dionosil



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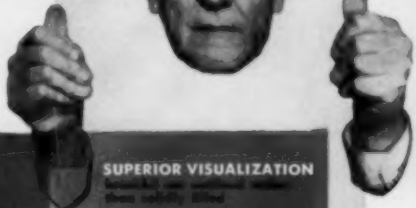

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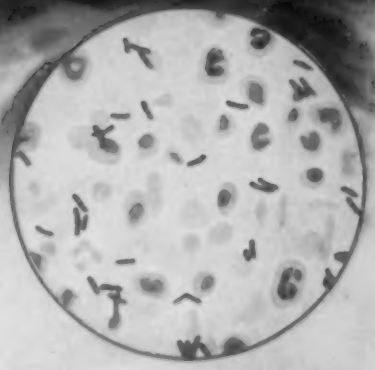

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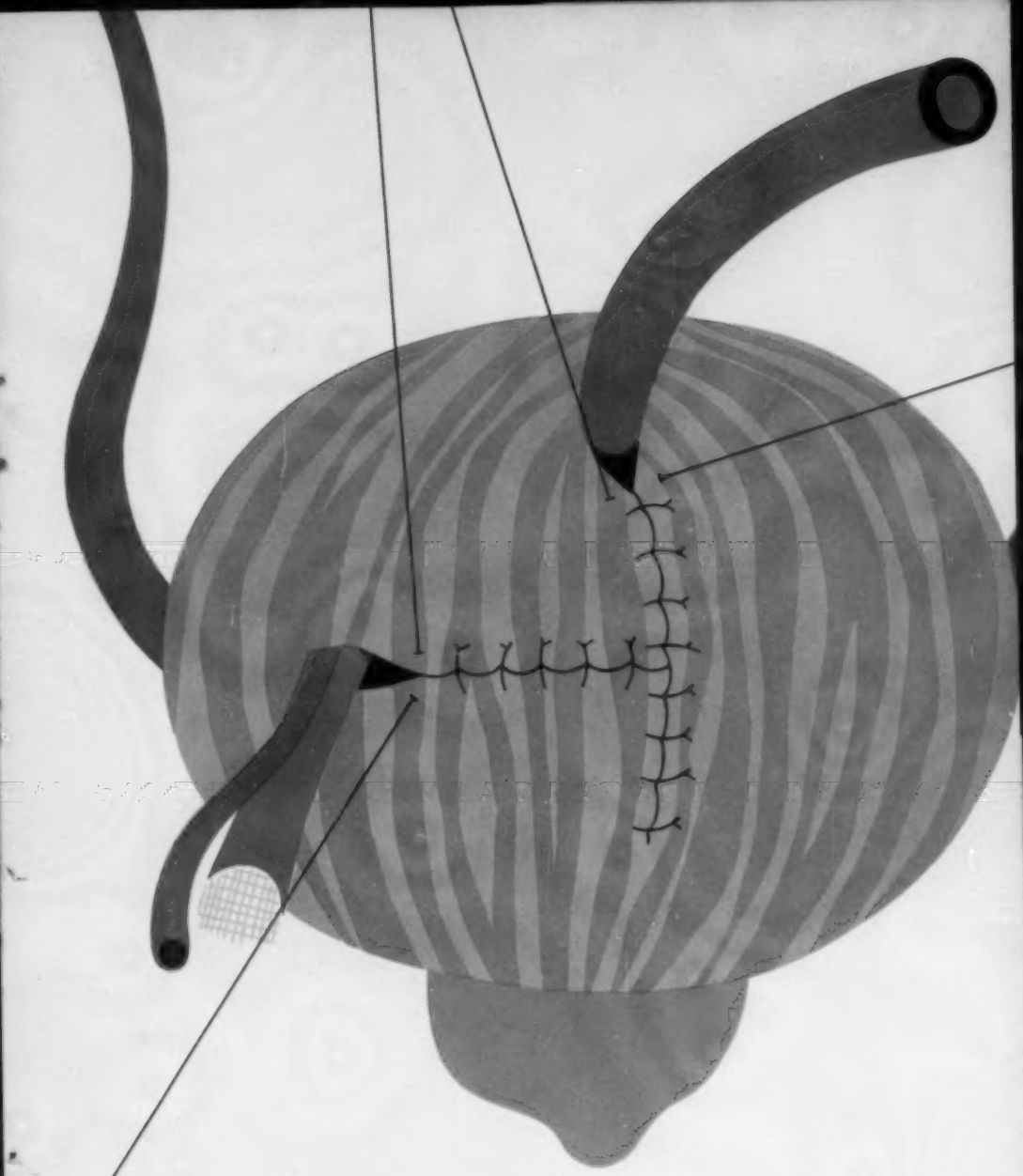

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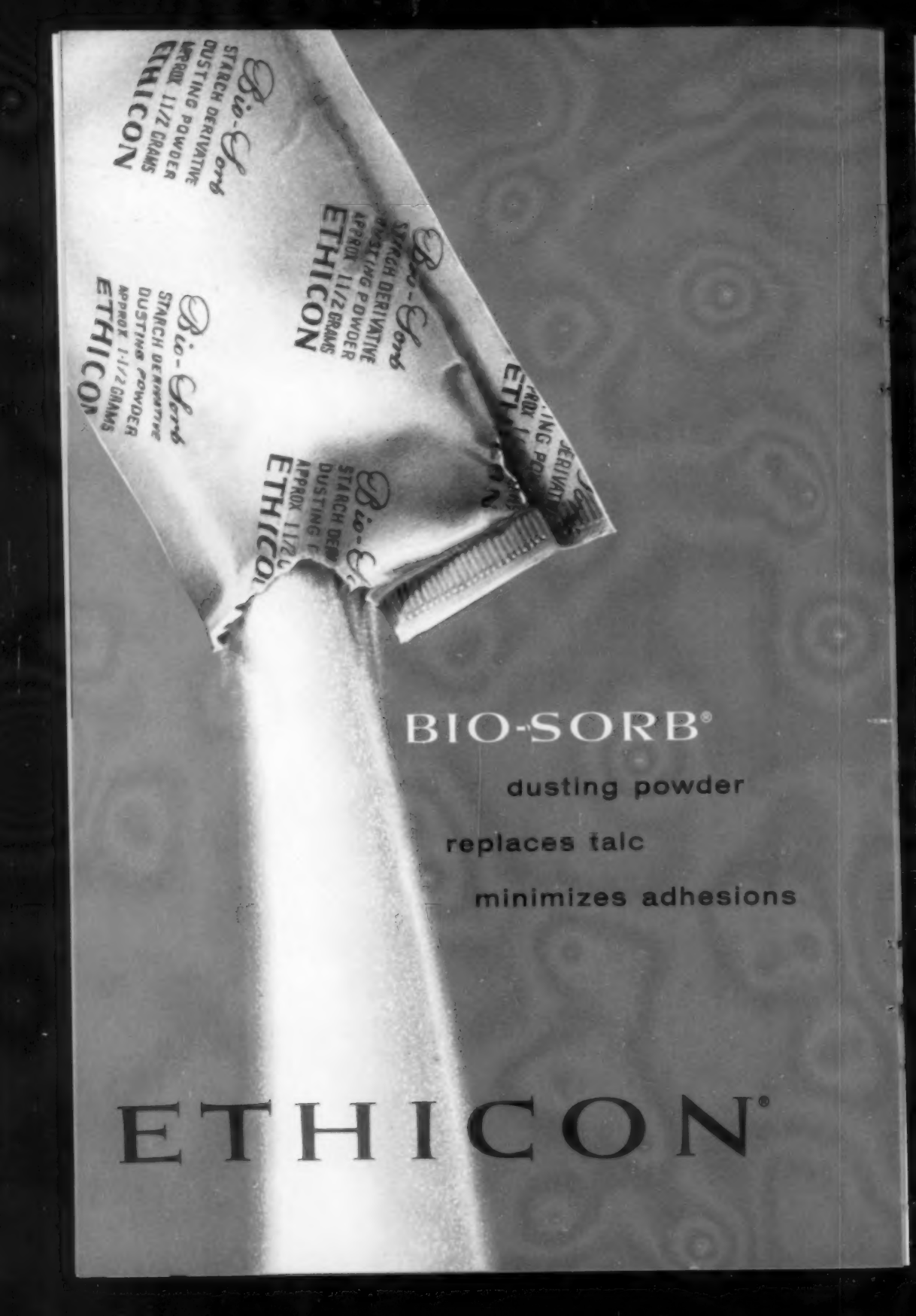
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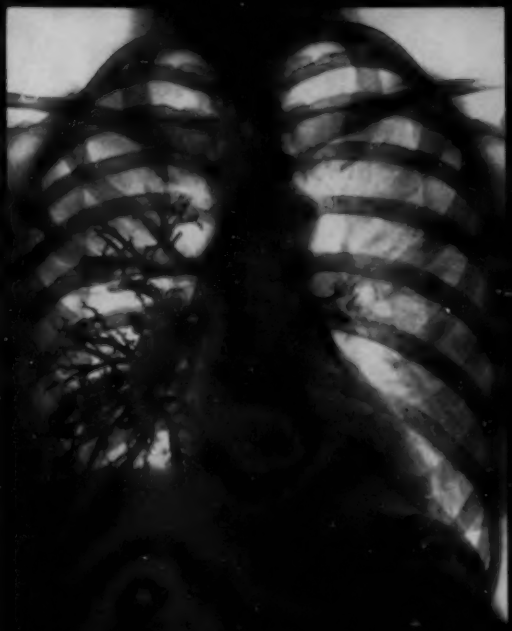
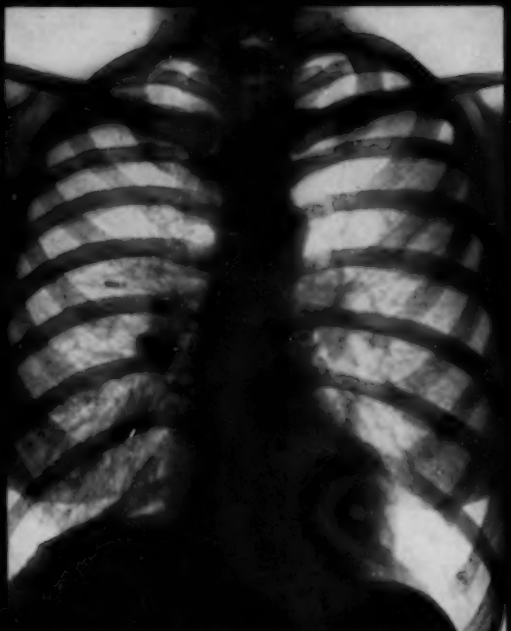


Bronchogram of right lung with VISCIODOL. Note clear outline of bronchi and absence of alveolar filling.



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1. Burrascano, J. J.: Sea View Hosp. Bull. *15*:149 (July) 1955.

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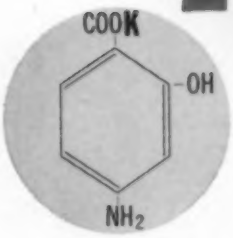

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1. *Molthan, L., Cohen, R. V., and Zarafonetis, C. J. D.: Clinical use of potassium para-aminosalicylate (KPAS). Am. Rev. of Tuberc. and Pulmon. Dis. 71:220 (Feb.) 1955.*

2. *Cohen, R. V., Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations). Read before the American Trudeau Society, Annual Meeting, Milwaukee, Wisconsin, May 23-27, 1955.*

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1. Camarata, S. J.; Jacobs, H. J., and Affeldt, J. E.: Read Before The Southern California Chapter of The American College of Surgeons, Palm Springs, Calif., January 23, 1953.
2. Miller, W. F.: New England J. Med. 251: 989, 1955.
3. Limber, C. R.; Reiser, H. G.; Roettig, L. C., and Curtis, G. M.: J.A.M.A. 149: 816, 1952.

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*Smessaert, Andre; Collins, V.J.; and Kracum, V.D.: *New York Jour. Med.*, 55:1587, June 1, 1955.

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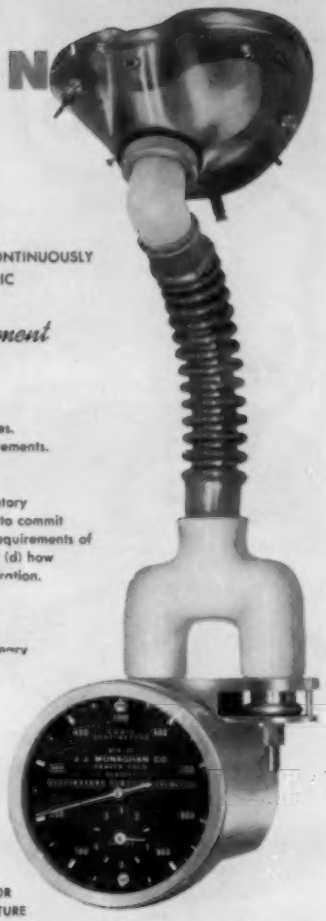

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DISEASES of the CHEST

VOLUME XXIX JUNE, 1956 NUMBER 6

Surgery for Pulmonary Cancer

A Declaration of Dividends

RICHARD H. OVERHOLT, M.D., F.C.C.P.* and JAMES A. BOUGAS, M.D.**

Boston, Massachusetts

Three- and five-year cures among individuals, once victims of pulmonary cancer, make up a constantly expanding group. A search for common factors in the extent, character and management of their disease was undertaken in these fortunate individuals.

Selected groups from a 23-year experience with over 1400 cases of primary lung cancer (excluding all cases of bronchial adenoma) serve as the basis for this report. Within the groups discussed, all cases are consecutive and all are histologically verified. All survival statistics are referred either to the total number of cases considered in each group or to all resections for a particular period of time. The follow-up of 683 verified cases to 1951 is complete with the exception of one case. There is a 93.5 per cent complete follow-up in cases first seen from 1951 to 1953. For statistical purposes, all cases not followed are considered dead. Operative mortality figures include all hospital deaths following induction of anesthesia for thoracotomy as well as all other deaths occurring from any cause within 30 days of surgery.

Extent of Cancer

To determine the extent of the cancer in patients who survived pulmonary resection five or more years, 588 cases of histologically verified cancer were studied. These cases were seen first during the 18-year period from 1932 to 1950. Two hundred and four (35 per cent) had resections with an overall mortality of 15 per cent. At the time of surgery, the cancer appeared localized to the lung in 39 per cent of the cases. Sixty-one per cent had tumors which had extended to the mediastinal lymph nodes or grossly to other thoracic structures. Of the 204 patients who had resections, 46 (23 per cent) survived five or more years without any evidence of recurrence. Several, in addition, survived three or more years, then died from other than causes attributable to their pulmonary disease, and necropsy demonstrated no evidence of residual carcinoma anywhere in the body. One of the 588 was lost to follow-up. His diagnosis had been verified by biopsy of a peripheral lesion and no thoracotomy was performed.

*Thoracic Surgeon, New England Deaconess Hospital; Director, Overholt Thoracic Clinic, Boston.

**Fellow in Thoracic Surgery, Overholt Thoracic Clinic, Boston.

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TABLE I
LUNG CANCER VERIFIED OVERHOLT THORACIC CLINIC 1932-1950

5 YEAR SURVIVORS — EXTENT OF INVOLVEMENT		
Total		588
Resected		204
5 Year Survivors 8 Per Cent of All Patients 23 Per Cent of Resected	46	
Localized	32	
Mediastinal L N Involved	10	
Gross Extension	4	

An unusual finding was that 14 (30 per cent) of the 46 five-year survivors were patients who had resections for cancers which had extended beyond the confines of the lung (Fig. 1A and 1B). These resections had been considered palliative. Surgery had been done to relieve patients of disabling symptoms with the additional hope that their lives might be prolonged. However, in some, an unenvisioned cure resulted. These represented an unexpected bonus of "palliative surgery."

Of 80 patients who had resections of cancers which had extended grossly outside the lung, four (5 per cent) survived five years or more. Of 44 patients who had resections of cancer which had spread to mediastinal lymph nodes, 10 (22 per cent) survived five years. Thirty-two (40 per cent) of the 80 patients with resections of localized pulmonary cancers lived five years (Table I). This survival rate in patients who had cancers extending outside the lung is very similar to the five-year survival of

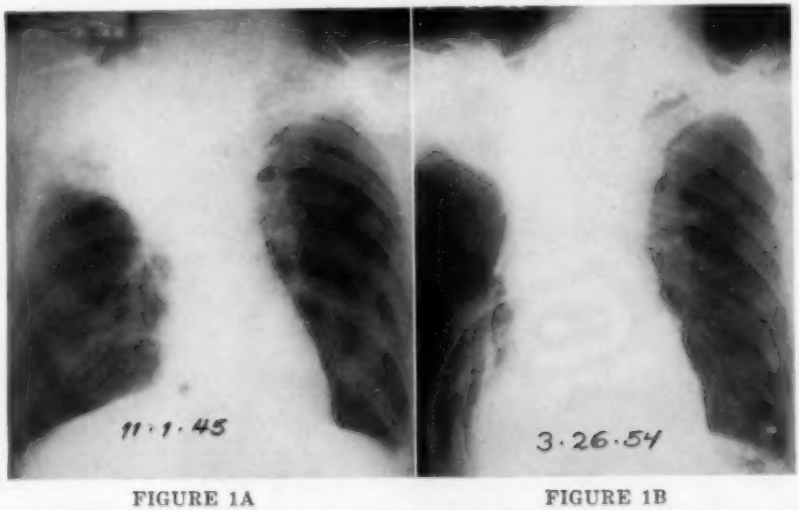


FIGURE 1A FIGURE 1B

Figure 1A: Mr. S. W., age 49. Pre-operative x-ray film showing right upper lobe lesion. Symptoms had been present for 18 months. Mediastinal involvement was anticipated, and found, due to the high location of the centrally placed epidermoid carcinoma.—*Figure 1B:* Mr. S. W. Post-operative x-ray film nine years 4 months after right pneumonectomy. During these years, patient has been well and there has been no evidence of recurrence.

"one in ten" reported in 1952 by Ochsner et al.[1] In striking contrast, however, is the experience of Churchill et al who reported in 1950 that no five-year survivors were found among patients with positive lymph nodes in the resected specimen.[2]

Fortunately, there are indications from the number of three- and four-year survivors that the extra dividend of five-year survivors from palliative resection may increase. Soon more five-year follow-ups will become available from patients who have undergone pulmonary and mediastinal lymph-node resection by the improved techniques of more recent years. Failure of x-ray therapy to prolong useful and comfortable life and a growing dissatisfaction with x-ray therapy for relief of symptoms other than of bone pain and superior mediastinal obstruction have given added impetus to attempts at surgical palliation (Table II). With the newer devices now available for postoperative care, more cases can be ambulated in three days and discharged from the hospital with a total stay of two weeks. This means that the expense, discomfort and disability may be far less with surgery than with supervoltage radiation or chemotherapy. Recently, excision has become a reasonable and more logical solution for palliation than heretofore and is used more frequently. The impact of excisional therapy on the bronchial obstruction and associated inflammatory factors is immediate. Cough disappears, breathing ability improves and often pain can be completely relieved for considerable periods of time. Radiation and chemotherapy can be used to complement or supplement

TABLE II
1941-50

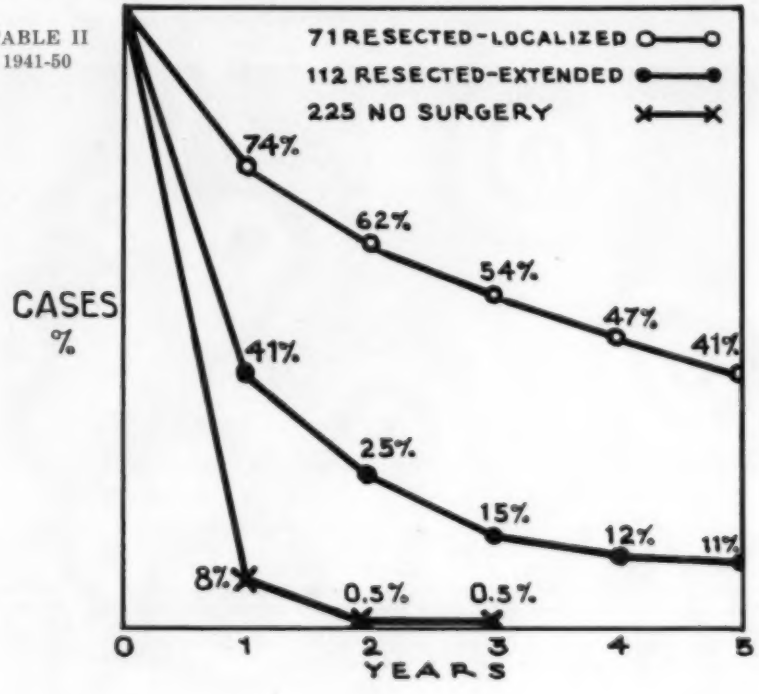


TABLE III:
LUNG CANCER VERIFIED OVERHOLT THORACIC CLINIC 1932-50

5 YEAR SURVIVORS — HISTOLOGY	
Total	46
Epidermoid	34
Undifferentiated	7
Adenocarcinoma	5

excisional therapy if and when metastatic disease progresses to demand further attempts at palliation.

Pathology

Although epidermoid carcinoma was the predominant lesion resected from the 46 patients who survived five years, more undifferentiated tumors and adenocarcinomas were found than had been anticipated. Thirty-four of the cancers were epidermoid; seven were undifferentiated; and five adenocarcinomas (Table III). Among the undifferentiated cancers were four with epidermoid and simplex foci, one of large-cell type, and two small-cell types. Two of the adenocarcinomas were bronchiolar carcinomas, apparently a more benign type of pulmonary cancer.[3, 4, 5] Three were well-differentiated adenocarcinomas. There was no evidence on careful study that these tumors arose from benign adenomas. The tumors of all histologic types ranged from one to eight centimeters in greatest diameter.

In 43 resected specimens where the location of the lesion could be established, 25 were located peripherally to the main lobar bronchi; 18 were

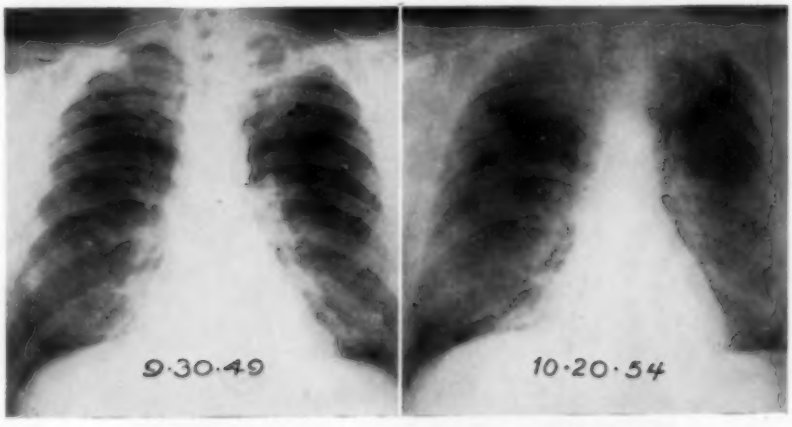


FIGURE 2A FIGURE 2B

Figure 2A: Mr. M. A., age 45. Symptoms of cough and occasional hemoptysis were present for five months. Pre-operative x-ray film revealed areas of cavitation in the left postero-apical segment. At thoracotomy in October, 1945, all mediastinal and hilar nodes were found to be negative. The involved segment was removed for total biopsy. The frozen-section report was chronic granuloma. Subsequently, permanent sections revealed undifferentiated carcinoma.—*Figure 2B:* Mr. M. A. A post-operative x-ray film five years and one month after a curative segmental resection. Patient is asymptomatic and actively engaged in business.

TABLE IV
LUNG CANCER VERIFIED OVERHOLT THORACIC CLINIC 1941-1952

	Number	Survived 3 years or more Per Cent	Number
Conservative Resection	24	29	(7)
Radical Resection	302	26	(78)
X-Ray Treatment	64	0	(0)

located centrally; 24 were in the upper lobe; 12 were in the lower lobe; six were encroaching upon the main-stem bronchi; and one was in the middle lobe.

The fact that one-fourth of all five-year survivors had resections for undifferentiated and adenocarcinomas is cause for definite encouragement.

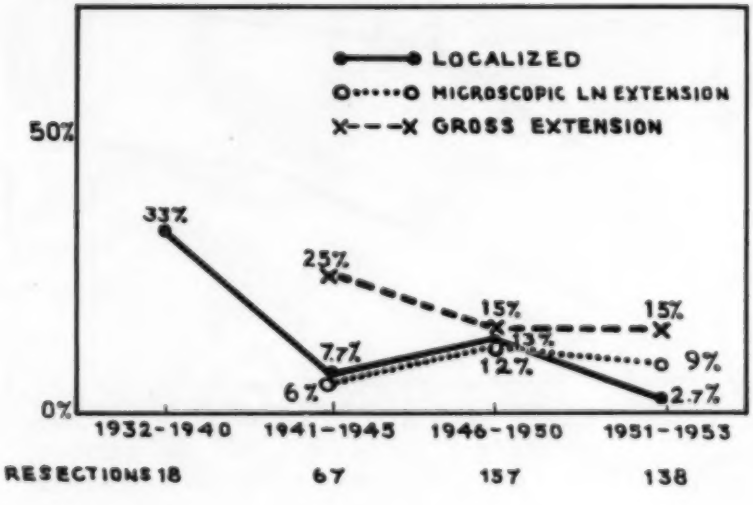
Extent of Resection

During the 12 years from 1941 to 1953, 42 segmental resections, lobectomies or bilobectomies were performed for primary verified lung cancer. In the same period, 327 pneumonectomies were done.

There were 40 operative deaths (12 per cent) among the patients who had pneumonectomies (38 per cent were for localized lesions and 62 per cent for lesions which had extended grossly or to mediastinal lymph nodes). By way of approximate comparison, there were four operative deaths (9.5 per cent) in the patients who had lobectomies (40 per cent of these were for localized lesions and 60 per cent were for lesions which had extended). One hundred and eight (33 per cent) of the patients who had pneumonectomy were known to be living more than one year since surgery. Twelve (29 per cent) of the patients who had lobectomy were alive more than one year.

A consideration of the resections performed between 1932 and 1952 permits a determination of three-year survival. In that period, 24 pa-

TABLE V

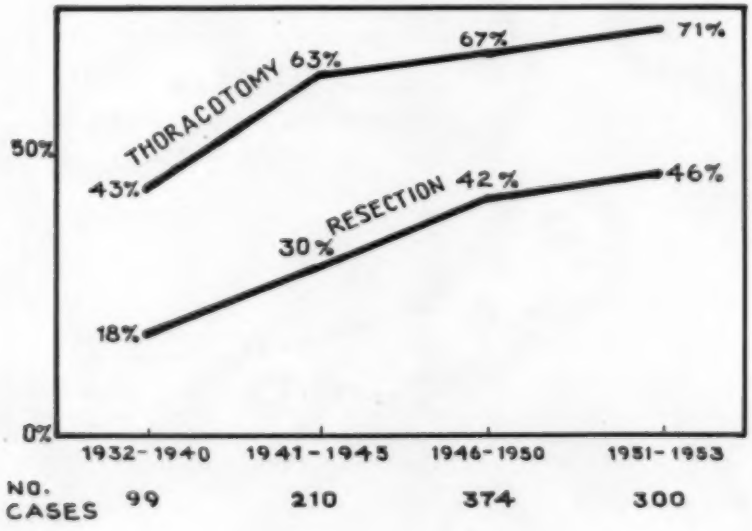


tients had lobectomies; seven (29 per cent) are living and well. Three hundred and two pneumonectomies were done; 78 (26 per cent) are alive and well. Sixty-four patients had x-ray therapy alone—some of them, two million volt x-ray, usually for advanced disease; none survived more than three years (Table IV).

It is not our intention here to present this small group of limited pulmonary resections as statistical evidence for or against the selection of such procedures in surgical therapy of primary pulmonary carcinoma. Rather, our purpose is to present this data as a necessary and thought-provoking "book-keeping" of surgical experiences in the field of lung cancer. We must agree with Churchill et al, that under carefully considered conditions, lobectomy may be a better procedure than pneumonectomy might be for the individual patient.

Our general policy in surgical therapy of lung cancer has been to achieve, whenever possible, a pneumonectomy with as extensive a resection of mediastinal lymph nodes as seems reasonable. Paratracheal nodes, carinal nodes, lymphatics in the inferior pulmonary ligament and lymph nodes from the contralateral side of the mediastinum have been removed. Intrapericardial ligation of pulmonary vessels is done when it facilitates the dissection or when partial pericardectomy is necessary to stay well beyond tissues invaded by the tumor. Surgical judgment in the individual patient prompted lobectomy in the occasional case. Palliation of clearly incurable cancer in patients with limited cardiac or pulmonary reserve was the most frequent reason for limited resection. These were performed to relieve the patient of incapacitating symptoms, such as, pain, infection or hemorrhage. In a few patients, it was felt that all the tumor could be removed by the limited resection. In two, only a segmental resection was

TABLE VI



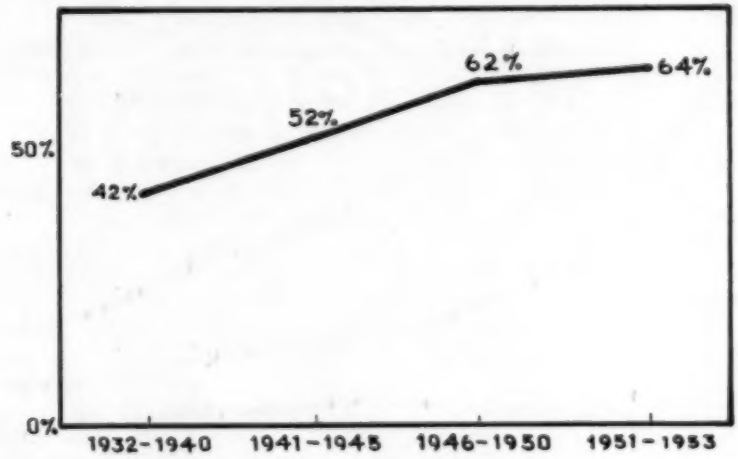
carried out (Fig. 2A and 2B). Some of the lobectomy cases had been followed by x-ray for several years and were undiagnosed until total biopsy was done by using the lobe as the unit for resection. A radical removal of mediastinal lymph nodes was also carried out. When lymph nodes resected from the mediastinum were reported negative for tumor on frozen-section examination and the physiologic age and cardiopulmonary function of the patient were considered, it seemed wise to avoid sacrifice of more pulmonary tissue. Also, we feel it extremely important not to do anything less than a total biopsy in any suspect case because of the danger of spilling tumor cells into the operative field.

With the improvement of resection techniques, anesthesia, blood banks, antibiotics and ancillary supportive services, the operative mortality has fallen steadily (Table V). Now, the period of palliative surgical extirpation of moderately and far-advanced lung cancer is maturing.

Thoracotomy and resection rates of patients arriving at our clinic have risen steadily (Table VI). Almost three-fourths of all the patients seen have been explored, and two-thirds of these have been found to be resectable (Table VII). Although statistics from a thoracic surgical clinic cannot be interpreted as a trend for the therapy of the disease as a whole, it is encouraging to see similar trends in clinics and hospitals elsewhere in the country.[1, 9]

Most encouraging has been evidence that now more patients are coming to thoracotomy earlier in the course of their disease. Patients and their families are more aware of the need for routine chest x-ray examinations. X-ray examination is being requested earlier and more frequently by practicing physicians. There is a fuller realization that negative cytology and negative bronchoscopy do not rule out malignancy. The delay at-

TABLE VII



	1932-1940	1941-1945	1946-1950	1951-1953
RESECTED	18	67	157	138
THORACOTOMY	43	129	253	214

tributable to physicians in the cases here reported has decreased from 11 to three and one-half months (Table VIII).

Of 30 patients with x-ray survey-discovered lung cancer seen at the Overholt Thoracic Clinic between December, 1947, and April, 1951, nine (30 per cent) survived three years.[10] This over-all survival is heartening, although fully one-third of the patients delayed their search for surgical therapy until striking symptoms caused them alarm. In recent years, the educational program concerning the cancer potential of the silent shadow is beginning to bear fruit. Of 16 silent cases explored within three months of the discovery film, all were resectable and 11 were found to be localized.

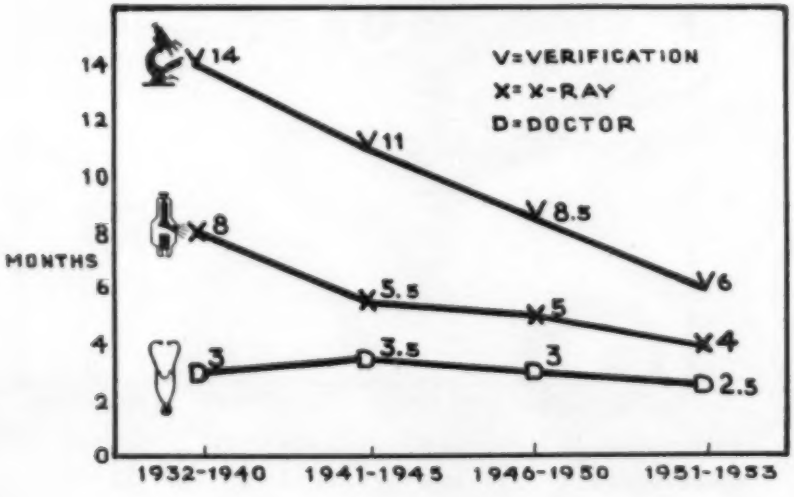
The gravity of the situation for the individual who harbors a carcinoma of the lung brings into sharper focus the more important issue—that of prevention. The cause of cancer is not known. The growing evidence that addiction over long periods of years to the inhalation of tobacco smoke is an aggravating factor cannot be overlooked.[6, 7, 8, 11] Doctors can well be advised to concentrate some of their efforts toward this problem as it may well lessen their burden of case-finding and therapy.

SUMMARY

Forty-six patients who survived five or more years after resection for pulmonary carcinoma have been discussed. Factors which relate to curability from this and an over-all experience with the management of patients between 1932 and 1953 are given.

Epidermoid cancer treated prior to gross or microscopic evidence of extension beyond the lung gives the best prognosis. The higher grades of malignancy (Undifferentiated, oat-cell, etc.) are not always hopeless. In fact, seven of the 46 five-year survivals were treated for malignancies of this type.

TABLE VIII



Palliative surgery may turn out to be curative. Over 10 per cent of those originally considered hopeless have been saved.

The extent of the resection must be based on the location and character of the lesion as well as upon the functional capacity of the contralateral lung. A limited resection has proved to be adequate and a preferable method of management for selected individuals

Higher cure rates can be predicted in the future as more explorations are done to determine the nature of lesions which produce silent abnormal densities in chest films.

RESUMEN

Se discuten los casos de cuarenta y seis enfermos que han sobrevivido el término de 5 o más años después de resección pulmonar por carcinoma. Se proporcionan los factores que están en relación con la curabilidad así como el resultado de la experiencia general en el tratamiento de enfermos de estos entre 1932 y 1953.

El cáncer epidermoide tratado antes de evidencia gruesa o microscópica de extensión fuera del pulmón, tiene el mejor pronóstico. Los de más elevada malignidad (no diferenciados, de células avenoides, etc.) no son siempre desesperados. De hecho, siete de las sobrevividas a los 5 años que son 46, se trataron por neoplasias malignas de ese tipo.

La cirugía paliativa puede resultar curativa. Más de 10 por ciento de los considerados desesperados se han salvado.

La extensión de la resección debe basarse en la ubicación y carácter de las lesiones así como en la capacidad funcional del otro pulmón. Una resección limitada ha demostrado ser adecuada y preferible para ciertos individuos.

Se pueden prever proporciones de curación más altas en el futuro a medida que se hagan exploraciones para determinar la naturaleza de las lesiones silenciosas que producen densidades asintomáticas en la película radiográfica.

RESUME

Les cas de 46 malades ayant survécu pendant cinq ans et plus, a une résection de cancer pulmonaire, ont ete discutés. On présente les facteurs ayant influé sur la curabilité de cette série ainsi que le compte rendu général sur le traitement des malades entre 1932 et 1953.

Le cancer épidermique traité avant qu'il y ait évidence pathologique ou microscopique d'une extention hors du poumon, a le meilleur prognostique.

La chirurgie palliative peut devenir curative. Plus de 10% des malades considérés comme perdus a l'origine, ont ete sauvés. Les degrés les plus avancés de malignité (non differenciées, microcellulaires, etc.) ne sont pas toujours sans espoir. En fait 7 de ces 46 malades ont ete traités pour des tumeurs de cette sorte, et ont survécu cinq ans.

L'extension de la résection doit être basée sur la location et le caractère de la lésion aussi bien que sur la capacité fonctionelle du poumon contralatéral. Il a ete prouvé qu'une résection limitée est suffisante et préférable pour certains malades.

On peut prédire un pourcentage plus élevé de guérisons dans l'avenir

si l'on tient compte du plus grand nombre d'explorations faites pour déterminer la nature des lesions asymptomatiques qui produisent des densites anormales sur les radios pulmonaires.

ZUSAMMENFASSUNG

Es wurden 46 Kranke, die 5 oder mehr Jahre nach einer Resektion wegen Lungen-Carcinom noch am Leben waren, besprochen. Die Faktoren, die zur Heilbarkeit beitragen, werden anhand der Erfahrungen aus diesem und dem gesamten Behandlungsmaterial zwischen 1932 und 1953 dargestellt.

Der Epidermoid-Krebs hat die beste Prognose, sofern er behandelt wird, bevor mit blossem Auge oder mikroskopisch eine Ausdehnung über die Lunge hinaus in Erscheinung tritt. Nicht immer sind die stärkeren Grade der Bösartigkeit (undifferenziert, Sichelzellen) hoffnungslos. Wurden doch 7 von den 46 Kranken, die die Fünfjahresgrenze überlebten, wegen bösartiger Tumoren dieses Types behandelt.

Eine palliative Operation kann sich als eine curative erweisen. Über 10% der ursprünglich als hoffnungslos betrachteten Patienten sind gerettet worden.

Die Ausdehnung der Resektion muss ausgehen sowohl von der Lokalisation und dem Charakter der Veränderung als auch der funktionellen Kapazität der kontralateralen Lunge. Für ausgewählte Einzelfälle hat sich eine begrenzte Resektion als entsprechend und als eine bessere Behandlungsmethode erwiesen.

Es ist möglich, ein grösseres Verhältnis von Heilungen für die Zukunft anzunehmen, da mehr Untersuchungen angestellt werden zur Bestimmung der Natur von Veränderungen, die zu stummen abnormen Verdichtungen auf Thorax-Röntgenaufnahmen führen.

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Indications for Commissurotomy in Mitral Stenosis

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The scope of medical management of the patient with valvular disease continually is being redefined as surgical procedures for correction of valvular defects are tried, improved, and finally accepted. Severe degrees of valvular obstruction are recognized to be incompatible with good health; surgical intervention is indicated as soon as the stenosis progresses to a point where it becomes a marked handicap to the patient, provided contraindications are absent or only minor.

We all are aware that a number of patients with narrowed mitral valves may—with adequate observation and proper medical management—live for many years in relative comfort, experiencing little distress except after unusual exertion. Some may even live out a relatively normal life span with little or no restriction in normal activity. In the majority of cases, however, cumulative effects of strain imposed by the mechanical stricture progressively handicap the heart until, eventually, work tolerance reaches extremely low levels, the patient becomes totally incapacitated, and premature death results. It is our problem, as cardiologists and internists, to sift out from the patients under our care those who will benefit from mitral surgery, and to determine when in the progressive series of events mitral surgery will most benefit the individual patient.

In order that we shall be able to choose the point at which surgical intervention will be most beneficial, it is necessary that we understand thoroughly the stages of progressive mitral stenosis, and that we recognize the signs and symptoms which indicate the status of the patient at any particular moment. If intervention is to be of the greatest value, it must come before irreversible changes in the heart and related structures occur, which will in themselves limit recovery and survival of the patient.

Progressive Stages

First overt symptoms of mitral stenosis are produced by the damming back into the lesser circulation of a volume of blood which can no longer flow normally from the left auricle into the left ventricle because of resistance of the narrowed orifice. To compensate for the narrowed opening and to maintain cardiac output at near-normal levels, pressure proximal to the mitral valve must increase. Initial indication of the puckering or tightening of the mitral orifice is the presence of selective left atrial hypertrophy, due to the diminished output of blood from the left atrium,

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together with increased pressure within that chamber, which represents a primary attempt of the circulation to maintain adequate cardiac output despite the narrowed opening. As the opening continues to narrow, pressures proximal to the opening must increase if blood flow is to remain adequate. Since no valves or other structures separate the distended cardiac chamber from the pulmonary capillaries, elevated pressures are transmitted first to adjust veins and capillaries, then throughout the entire pulmonary vascular bed. Episodes of acute left atrial failure, characterized by the sudden onset of pulmonary edema, may occur. With the development of pulmonary hypertension, the prominent symptoms of mitral stenosis make their appearance — dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and other evidences of pulmonary congestion.

If the mitral orifice continues to narrow until the valve opening is reduced to only about one-fifth its normal area, a compensatory narrowing of the arterioles and the smaller arteries in the lung occurs, represented histologically by intimal proliferation and medial hypertrophy.[1] At this point, marked differences may be noted in individual reaction to the altered hemodynamics.

The patient may never develop pulmonary resistance to a degree sufficient to prevent overflooding of the pulmonary vasculature; symptomatology then will continue to be primarily that of pulmonary congestion. Or, moderate pulmonary resistance may develop, with a lowered output of blood entering the lung at a rate commensurate with its movement through the mitral valve; if so, the major symptoms are fatigue, weakness and exhaustion—a result of the lowered cardiac output.[1]

However, in some patients pulmonary resistance may climb to 15 to 20 times the normal, and the blood is unable to gain entrance to the lung at the rate it escapes through the mitral valve. In such cases, the right ventricle becomes markedly enlarged and fails—a condition reflected in engorgement of the liver, increased venous distention, and, finally, salt and water retention (edema).

These differences in individual adjustment to the mitral block are most important, for progressive adaptation to the altered circulation may relieve for a time the symptoms most indicative of the disorder, i.e., the symptoms of pulmonary congestion.[1] We must not be misled into accepting these changes as signifying spontaneous improvement in the course of its disorder; rather, we must recognize them for what they are—signs of the progressive march of the disease to its final and inevitable conclusion. Thus, for example, disappearance of episodes of frank pulmonary edema cannot be interpreted as a melioration of the patient's condition; probably, pulmonary vascular resistance merely has developed to a point where it protects against sudden flooding of the lungs by surges in cardiac output under conditions of stress, tachycardia or increased blood volume.

Diagnosis of Mitral Stenosis

The diagnosis of mitral stenosis poses no problem for the internist once the narrowing has progressed to a point where the constriction interferes noticeably with the circulation. In relatively pure stenosis, the left

atrium is distended; the left ventricle, which receives a strangulated blood flow, is reduced in size; and the entire lesser circulation is slowed correspondingly as the blood makes its way through the impaired opening.[2] In patients with regular heart rhythm, both left auricular pressure and pulmonary venous pressure are exaggerated in auricular systole. Ventricular diastolic filling is accompanied by the typical stenotic murmurs.[2]

Rarely, conditions are present which mimic mitral stenosis. Chronic failure of the left ventricle, for example, which also results in elevations of venous, capillary and arterial pressures, might be confused with the more common stenosed valve if the clinician were to depend too heavily upon these measurements and if he failed to place sufficient emphasis on roentgenologic and electrocardiographic signs of left ventricular hypertrophy. Constrictive pericarditis, if limited chiefly to the left side, may interfere with left ventricular excursion in diastole, or may partially obstruct the pulmonary veins; even if bilateral, constrictive pericarditis may effect the lesser circulation and the right ventricle similarly to mitral stenosis. Congenital or acquired stenosis of the pulmonary veins may have the same effects.[3] A pedunculated tumor of the left atrium may obstruct the mitral orifice;[4] again, in an occasional case, a free thrombus may cause intermittent obstruction of the mitral valve in a ball-valve fashion.[3] In the latter two instances, the intermittent nature of the symptoms and the changing physical signs would serve to differentiate the conditions from true mitral stenosis.

Other conditions which may simulate mitral stenosis are hyperthyroidism and interatrial septal defect. The findings of normal or nearly normal pulmonary capillary pressure on cardiac catheterization in a patient having "typical" murmurs of mitral stenosis would be suggestive of a defect in the atrial septum.[3] The diagnosis of interatrial septal defect would receive support from the observation of arterialization of the blood in the right atrium.[3]

Diagnostic Measures

The internist has many tools on which to base his diagnosis of mitral stenosis. These tools serve also to determine whether or not complicating conditions exist which would make commissurotomy unusually hazardous or contraindicate the operation altogether.

Laboratory examinations are used to detect possible rheumatic activity or the presence of subacute bacterial endocarditis. Recent or recurrent rheumatic infection generally is accepted as an absolute contraindication to surgery. Not only may commissurotomy cause an exacerbation or recrudescence of the disease, but episodes of rheumatic fever following surgery may reseal the opened commissures and thus negate the results of surgery. Resealing of the valves occurred in only two cases under our care; in both instances, vegetations secondary to episodes of rheumatic fever were responsible. This is one reason we prefer to wait until our patients have been free from rheumatic activity for a number of years, or have passed the age when rheumatic episodes are likely to recur, before attempting commissurotomy. Subacute bacterial endocarditis, too, is a

temporary contraindication, which must be eradicated by antibiotics before surgery is performed.

Cardiac size and configuration may be studied and the size of individual chambers of the heart can be estimated by percussion, cardiac fluoroscopy, teleoroentgenograms and esophagrams; through palpation of the apex beat, or through angiocardiography; and by means of unipolar lead electrocardiography.

Murmurs at the mitral orifice may be studied by means of auscultation and phonocardiography; thrills may be palpated. Early physiologic changes may be detected either by measures of circulation time or by estimations of cardiac output both at rest and after exercise, as calculated by cardiac catheterization. In questionable cases, electrokymography and pulmonary capillary venous tracings obtained at cardiac catheterization may be used to gain additional evidence as to pressure and volume changes in the pulmonary artery and the right ventricle. Systolic pressures of 50 mm. mercury within the pulmonary artery may represent the critical level above which the patient must shortly expect serious consequences.[5]

Accuracy in predicting the presence, character and extent of multivalvular lesions has been increased through the technic of direct entry into the left side of the heart, as described in a series of articles published during 1953 and 1954 by Bjork and his co-workers.[6] Left heart catheterization allows measurements of pressure in the aorta, the left ventricle and the left atrium, and thus yields more information than was heretofore possible in the evaluation of valvular lesions and feasibility of surgical correction of these lesions.

Complicating Factors

I spoke earlier of the use of diagnostic tools in determining whether or not complicating conditions exist which would make commissurotomy unusually hazardous, or which contraindicate operations altogether. Preferably, the lesion should be a "pure" stenosis; ideally, only left atrial and right ventricular enlargement should be present. Associated valvular lesions, if present, should be minimal; and mitral insufficiency, either absent or insignificant in amount.

Probably the greatest difficulty is experienced in differentiating between predominant mitral stenosis and predominant mitral insufficiency and —if insufficiency is present—in gauging its severity. In mitral stenosis the left atrium is distended, but the left ventricle remains small. In mitral regurgitation, the entire left side of the heart is enlarged—the auricle because it is filled both by regurgent blood flow through inefficient mitral valve and by emptying of the pulmonary veins;[2] and the ventricle, in an attempt to secure adequate aortic output despite the inefficient valve. A markedly enlarged left atrium suggests a sizeable degree of mitral insufficiency,[7] particularly if dilation of the auricle is visible in ventricular systole during fluoroscopic examination of the heart. The backward jet through the incompetent valve causes a systolic murmur and a systolic pressure wave in the auricle and pulmonary veins[2] which, when sinus rhythm is present, is expressed as a marked deflection in the pulmonary

capillary tracing. Rapid ascent and descent of the limbs of the tracing also are characteristic of mitral insufficiency.[7]

Left ventricular enlargement often is associated with aortic insufficiency or with systemic hypertension, as well as with mitral insufficiency. Under any of these conditions, commissurotomy usually is contraindicated.

Aortic stenosis is reflected in the duration of systole on a brachial arterial pressure tracing; aortic insufficiency, in lowered diastolic blood pressure.[1] An enlarged, pulsating liver should lead one to suspect the presence of tricuspid insufficiency; and a stenosed tricuspid valve is suggested by the continuance of pronounced edema and ascites and an elevated venous pressure in spite of vigorous medical therapy.[1] Trace, Bailey and others[8] suggest that the existence of tricuspid stenosis may be confirmed by the demonstration of both large "a" and "v" waves in the liver pulse tracing, especially when normal sinus rhythm is present.

Diagnostic Limitations

If we are to make the best use of the available diagnostic tools, we must be aware of their limitations. None of the commonly accepted clinical criteria are sufficiently exact to stand alone in the selection of patients for mitral surgery. Reliance on murmurs alone will often result in incorrect conclusions as to the circulatory dynamics, and may deprive suitable candidates for surgery of their best opportunity for restoration of function.

Ofttimes, neither percussion nor chest roentgenography will permit one to distinguish between right and left ventricular hypertrophy. Likewise, displacement of the apex beat downward and to the left does not necessarily indicate left ventricular enlargement, for such displacement can be produced by marked enlargement of the right ventricle.[7] Even when the apex beat is not so displaced, it may be hidden behind a rib and be hard to evaluate.[2]

Electrocardiographic findings are contributory only if they indicate the unusual. Thus normal unipolar leads do not rule out the presence of ventricular hypertrophy, but hypertrophy demonstrated in such leads yields valuable information.[2]

It is better for the clinician to place his reliance on a constellation of findings, rather than to rely too heavily on a single finding.

Factors Determining Operability

If satisfactory relief from the handicap of mitral stenosis is to be obtained without undue risk to the patient, it is necessary that the patient be a fair surgical risk, that his lesion be primarily stenotic, and that his myocardium—strained though it may be from overwork—be capable of restoring normal cardiac output once it is relieved of the undue strain imposed by blockage of the pulmonary outflow. It is immediately apparent, therefore, that the heart with enlargement of all chambers (which signifies rheumatic myocardial fibrosis), intractable right heart failure of considerable duration, and extreme debility are contraindications to operation. If long-standing pulmonary hypertension has lead to arterio- or atherosclerosis which is manifested by a high vascular resistance on cardiac

catheterization, and if the patient shows evidence of uncontrollable right ventricular failure with tricuspid insufficiency, engorgement of the liver, ascites and edema, little can be expected from commissurotomy.[9] Approximately three per cent of our patients died during or immediately after the operation: except for cases in which thromboemboli were a factor, death was due in almost every instance to pulmonary insufficiency which would not permit the undisturbed lung to take over respiratory function for even the period of operation.

Significant multivalvular disease constitutes a contraindication to operation at present, as does a marked degree of mitral insufficiency. Nevertheless, great strides are being made in cardiac surgery, and surgical repair of aortic stenosis probably will be accomplished with reasonable safety in the near future. Surgical attack on tricuspid stenosis also has begun, with satisfactory results reported in several instances.

We no longer regard age *per se* as a contraindication to operation: save for waiting until recurrence of rheumatic activity is no longer likely, we judge each case on its own merits and do not deny operative help to persons because they have passed an arbitrary age.

Auricular fibrillation is no bar to operation provided it has been brought under control. However, the presence of ventricular dysrhythmias or arrhythmias are absolute contraindications.[10]

Thromboembolism is not a bar to operation; rather it constitutes a strong argument in favor of commissurotomy, since ablation of the left appendage and improvement in cardiac output lessens the danger of thromboembolic episodes subsequent to commissurotomy.[11, 12]

Anticoagulant therapy is given to these patients to discourage formation of additional thrombi; during operation, prothrombin time is kept at 50 per cent of normal. Any thrombus within the auricular appendage can be controlled readily by a non-crushing clamp applied across the base of the auricular appendage.

Calcification of the mitral valve is no longer considered a contraindication to surgery. Although a definite danger exists that small segments of calcified plaque may be broken off during manipulation of the valve, umbilical tapes placed about the right innominate and left carotid arteries during the operation as a safety precaution protect the cerebral vessels from possible emboli, which are swept past the mouths of these vessels into small peripheral vessels.[13] Actually, the calcified valve fractures more readily than if the leaflets were pliable.[11]

Women with mitral stenosis who are within the child-bearing age and have had heart failure with a previous pregnancy may undergo commissurotomy as a prophylactic measure if they desire to have additional children, even though they are not disabled following pregnancy.[11]

Physical Fitness: A Major Criterion

From our experience, there seems little justification for using the operation as a prophylactic procedure early in the disease, before the stenosis has become an actual handicap. Excellent results were obtained in approximately 35 per cent of the 406 patients who underwent com-

missurotomy, good results in 30 per cent, and little improvement in an additional 30 per cent. Mortality rate in our series was only three per cent.

In determining whether the time has come to recommend surgical enlargement of a stenosed mitral valve, the clinician considers three factors: the degree of chronic disability of the patient; the improvement, if any, in the patient's condition as a result of proper medical management; and the speed with which the patient's condition is deteriorating. Periodic assessment of the patient's work-tolerance will furnish the answer to all three questions. Persons in class III of the American Heart Association's classification of functional capacity, or persons in class II but rapidly approaching class III are the best candidates for surgery.

At the time that surgical correction of mitral stenosis was a comparatively new and untried procedure—when the mortality was high and the risk grave—we hesitated to submit to surgery patients whose condition had deteriorated into class IV and who were totally incapacitated and confined to their beds unless they could be fully compensated and, for a short time at least, returned to class III.[13] Today, however, provided the services of a competent anesthesiologist fully conversant with and capable of coping with crises that may arise during cardiac surgery are available, we are less inclined to deny the benefits of surgery even to patients who can not be returned temporarily to class III, provided that failure of other organs secondary to the primary disease has occurred. For, without surgery, nine in ten such patients will die in the next twelve-month period, and over 65 per cent can be saved by the operation.[14] The welfare of the individual patient is more important than the box score.

SUMMARY

In the majority of cases, cumulative effects of strain progressively handicap the heart until the patient becomes totally incapacitated. If intervention is to be of greatest value, it must come before irreversible changes in heart and related structures occur, which will in themselves limit recovery and survival of the patient.

Progressive adaptation to the altered circulation may relieve for a time symptoms most indicative of the disorder; the physician must not be misled into accepting these changes as signifying improvement. In relatively pure stenosis, the left atrium is distended and the entire lesser circulation slowed. In patients with regular heart rhythm, both left auricular pressure and pulmonary venous pressure are exaggerated in auricular systole. Ventricular diastolic filling is accompanied by typical stenotic murmurs.

Conditions which mimic mitral stenosis include chronic failure of the left ventricle, constrictive pericarditis, congenital or acquired stenosis of the pulmonary veins, pedunculated tumor of the left atrium, a free thrombus which causes intermittent obstruction, hyperthyroidism, and interatrial septal defect. Laboratory examinations are helpful for detection of rheumatic activity or subacute bacterial endocarditis (both contraindications to surgery).

Cardiac size and configuration may be estimated by percussion, cardiac fluoroscopy, teleroentgenograms and esophagrams; through palpation of

the P.M.I. or through angiocardiography; and by means of unipolar lead electrocardiography. Murmurs may be studied by auscultation and phonography. Other useful measures are circulation time and estimations of cardiac output both at rest and after exercise, by ballistocardiography and cardiac catheterization (including direct entry into the left side of the heart).

For the present, multivalvular lesions are considered inoperable. Preferably, the operation should be performed when the patient is in class III (functional capacity) or in class II but rapidly approaching class III. The most important factor in scheduling the operation is the rate with which the patient's condition is deteriorating.

RESUMEN

En la mayoría de los casos los efectos acumulativos del esfuerzo dañan progresivamente el corazón hasta que el enfermo se incapacita totalmente. Si se espera que la intervención sea del mayor valor debe llevarse a cabo antes de que aparezcan cambios irreversibles en el corazón y en estructuras en relación con él, lo que limitaría la recuperación y la sobrevida.

La adaptación progresiva de la circulación alterada puede aliviar por algún tiempo los síntomas más relevantes de la afección; el médico no debe engañarse aceptando tales cambios como mejoría. En la estenosis relativamente pura el atrio izquierdo está distendido y toda la circulación menor es más lenta. En los enfermos con ritmo cardiaco regular, tanto la presión auricular izquierda como la presión venosa pulmonar están exageradas durante la sístole auricular. E llenado ventricular diastóloci se acompaña de los murmullos este nóticos típicos.

Las afecciones que imitan la estenosis mitral incluyen la insuficiencia crónica del ventrículo izquierdo, la pericarditis constrictiva, la estenosis congénita o adquirida de las venas pulmonares, el tumor pedunculado del atrio izquierdo, un trombo libre que cause obstrucción intermitente, el hipertiroidismo, y el defecto del septum interatrial. Los exámenes de laboratorio ayudan para el descubrimiento de la actividad reumatismal o de la endocarditis bacteriana aguda (ambas contraindicaciones de la cirugía).

El tamaño del corazón y la forma pueden ser estimadas por percusión, la fluoroscopía cardiaca, teleradiografías, y esofagogramas, por la palpación del choque de la punta o por angiocardiografía así como por la electrocardiografía unipolar. Los ruidos pueden estudiar se por auscultación y por fonografía. Otros recursos útiles son el tiempo de la circulación y estimaciones del rendimiento cardiaco tanto en reposo como después del ejercicio por la balisto-cardiografía y la cateterización cardiaca (incluyendo la entrada directa dentro del lado izquierdo del corazón).

Actualmente las lesiones multivalvulares se consideran inoperables. Preferiblemente la operación debe hacerse cuando el enfermo está en la clase III (Capacidad funcional) o en clase II que se aproxima rápidamente a la clase III. El factor más importante para determinar la operación es la rapidez con que el enfermo está empeorando.

Los clínicos se enfrentan a tres problemas en el diagnóstico y tratamiento

de la enfermedad cardiaca secundaria a disfunciones pulmonares: primero, el descubrimiento de los primeros síntomas clínicos de hipertensión pulmonar; segundo, la determinación de la afección definida o afecciones responsables de esa hipertensión y de la corrección de las afecciones en lo posible; y tercero, el tratamiento de los síntomas cardiacos. Deseo recalcar otra vez la importancia de determinar la causa primaria de la hipertensión pulmonar antes de que se emprenda cualquier tratamiento.

RESUME

Dans la majorité des cas, les effets accumulés du surmenage altèrent progressivement l'état du coeur et le malade devient totalement incapable d'activité. Si une intervention doit être la plus efficace possible, il faut qu'elle soit exécutée avant l'apparition des altérations cardiaques irréversibles et de leurs conséquences qui limitent la guérison et la survie du malade.

Une adaptation progressive aux troubles de la circulation peut permettre de supporter pendant un certain temps les manifestations les plus marquantes du désordre mais le médecin ne doit pas être induit en erreur et ne doit pas les considérer comme traduisant une amélioration marquée. Dans la sténose relativement pure, l'oreillette gauche est distendue et la petite circulation complètement ralentie. Chez les malades qui ont un rythme cardiaque régulier, la pression auriculaire gauche et la pression de la veine pulmonaire sont l'une et l'autre simultanément augmentées pendant la systole auriculaire. L'emplissage diastolique du ventricule est accompagné de bruits d'auscultation caractéristiques de la sténose.

Les états qui simulent la sténose mitrale sont l'insuffisance chronique du ventricule gauche, la péricardite constrictive et la sténose congénitale ou acquise des veines pulmonaires la tumeur pédonculée de l'oreillette gauche, le thrombus libre qui occasionne une obstruction intermittente, l'hyperthyroïdisme et l'altération de la paroi de l'oreillette. Les examens de laboratoire sont utiles pour mettre en évidence l'activité rhumatismale ou une endocardite microbienne subaiguë (toutes étant des contre-indications à l'intervention).

La dimension et la configuration du coeur peuvent être évaluées grâce à la percussion, à l'examen radioscopique, aux examens radiographiques avec exploration oesophagienne, à la palpation et à l'angiocardiographie, et à l'électrocardiographie unipolaire. Les bruits cardiaques peuvent être étudies par l'auscultation et la phonographie. D'autres mesures utiles sont le temps de circulation, l'évaluation du débit cardiaque à la fais au repos et après exercice par ballistographie, et le cathétérisme cardiaque (y comprios l'entrée directe dans la cavité gauche du coeur).

Actuellement les lésions multivalvulaires sont considérées comme inopérables. De préférence, l'intervention devrait être pratiquée lorsque le malade appartient à la catégorie 3 (capacité fonctionnelle) ou à la catégorie 2 mais se rapprochant rapidement de la catégorie 3. Le facteur le plus important pour les prévisions opératoires est le degré de l'altération de l'état du malade.

ZUSAMMENFASSUNG

In der Mehrzahl der Fälle wird das Herz durch sich häufende Belastungen zunehmend geschädigt, bis der Patient vollkommen belastungsunfähig wird. Ein Eingreifen ist *dann* von grösstem Wert, wenn es vor irreversiblen Schädigungen des Herzens und verwandter Gewebe, die per se die Genesungs- und Überlebensmöglichkeit des Patienten einschränken, geschieht.

Zunehmende Gewöhnung an die veränderte Zirkulation kann eine Zeitlang Symptome, die auf eine Strörung hinweisen, verschleiern; der Arzt darf nicht irregeführt werden, diese Verändrungen als Zeichen einer Besserung anzusehen. Bei isolierter Stenose ist der linke Vorhof erweitert und der gesamte kleine Kreislauf verlangsamt. Bei Patienten mit regelmässiger Herzaktion ist sowohl der Druck im linken Vorhof als auch in den Pulmonalvenen in der Vorhofsystole erhöht. Die diastolische Füllung des Ventrikels ist von typischen stenotischen Geräuschen begleitet.

Veränderungen, die eine Mitralstenose vortäuschen, können sein: chronisches Versagen des linken Ventrikels, konstriktive Perikarditis, angeborene oder erworbene Stenose der Pulmonalvenen, gestielter Tumor des linken Atrium, freier Thrombus, der intermittierenden Verschluss bewirkt, Hyperthyreose und Vorhofseptum-Defekt. Laboratoriumsuntersuchungen sind zur Aufdeckung eines aktiven rheumatischen Prozesses oder einer subakuten bakteriellen Endokarditis, die beide Kontraindikationen gegen einen chirurgischen Eingriff darstellen, von Nutzen.

Die Herzgrösse und die Herzfigur können durch Perkussion, Durchleuchtung, Röntgen-Fernaufnahme und Schluckakt bestimmt werden; durch Palpation des P.M.I. oder durch Angiokardiographie und durch unipolare Elektrokardiogramm-Ableitung. Die Geräusche können durch Auskultation und Phonokardiographie untersucht werden. Andere brauchbare Untersuchungen stellen die Messungen der Kreislaufzeit und des Herzminutenvolumens sowohl in Ruhe als nach Belastung mittels Ballistokardiographie und Herzkatheterisierung (einschliesslich des direkten Zuganges zum linken Herzen) dar.

Zur Zeit werden Veränderungen an *mehreren* Herzklappen als inoperabel angesehen. Die Operation sollte vorzugsweise durchgeführt werden, wenn der Patient sich in der Klasse III (Funktionskapazität) oder in Klasse II mit rascher Annäherung an Klasse III befindet. Am wichtigsten für die Planung der Operation ist der Zeitfaktor hinsichtlich der Verschlechterung des Krankeitszustandes.

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Intermittent Positive Pressure-Aerosol Therapy in Pediatrics*

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Introduction

For the past three years the Pediatric Research Department of the Lovelace Foundation has been engaged in investigative and clinical studies of the use of intermittent positive pressure breathing (hereinafter termed IPPB) therapy in the field of pediatrics. Studies in infant resuscitation[1] have proved its worth in (1) expanding the non-expanded lungs of newborns who do not breathe at birth, (2) assisting in the correction of partial atelectasis and anoxia, and (3) promoting bronchial drainage, and preventing infection and resorption atelectasis.

The demonstration of the effectiveness of IPPB in pulmonary conditions in adults by Motley, et al.[2] raised the question of whether this type of therapy might be beneficial to children with respiratory problems, and whether by early treatment we might be able to restore normal pulmonary function in this younger age group. The physiologic basis here for IPPB was to (1) provide uniform alveolar aeration with improvement in blood-gas exchange, (2) overcome spasm and promote bronchial drainage with decrease in irritation and infection, and (3) provide breathing exercise with improvement in muscle tone and compliance.

Plan of Investigation

Routine Studies—Children, ranging in age from one to 17 years, and suffering from various respiratory conditions, were included in the investigative studies. Routine studies consisted of thorough history and physical examination, complete blood count, throat or sputum culture with sensitivities, x-ray films of the chest and sinuses, and allergenic skin tests.

Pulmonary Function Tests—Pulmonary function tests included studies of the air flow, lung volumes, and intrapulmonary mixing and distribution. These tests gave the required objective information, since 99 per cent of pulmonary impairment in children is in ventilation, with less emphasis on diffusion. A ventilation chart was devised to simplify factor-impairment-cause relationship.

Obstructive, restrictive and dynamic impairment was easily and rapidly visualized by pneumotachographic studies, employing a flow orifice as previously reported.[3] Timed vital capacities gave an accurate estimate of the extent of obstruction. Spirograms during quiet breathing and max-

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imal inspiration and expiration (vital capacity) provided information on the bellows function of the lungs and chest (restrictive impairment). Residual volume determined by the open circuit method and combined with the spirogram provided *total lung capacity* and relative subdivisions.

Mixing and distribution was determined by means of a nitrogen meter from the clearance of pulmonary nitrogen when breathing oxygen. The total ventilation required to reduce the nitrogen in the expired gas to 1 per cent was measured. The nitrogen clearance ratio was computed by dividing the total clearance ventilation by the functional residual capacity. The nitrogen clearance equivalent or (ratio) thus obtained is a measure of ventilatory efficiency independent of lung volume. (Nitrogen clearance methods published elsewhere in detail).[4]

Role of Psychotherapy—It is recognized that many allergic conditions in children may be associated with emotional problems. Therefore, many of these children were referred to the Clinical Psychology Department for aid. Psychometric tests included: (1) Intelligence (Wechsler Intelligence Scale for Children), (2) Achievement (arithmetic, spelling, reading), (3) Personality and Projective Tests (drawing of a man and a woman, Roger's Personality Test), (4) Apperception (Children's Apperception Test or CAT, Thematic Apperception Test or TAT) and (5) Play Observation.

To simplify treatment and to promote interest and continuity of therapy, children with respiratory conditions received their IPPB in a special room called the Jet Room, so named by themselves, and from the ceiling

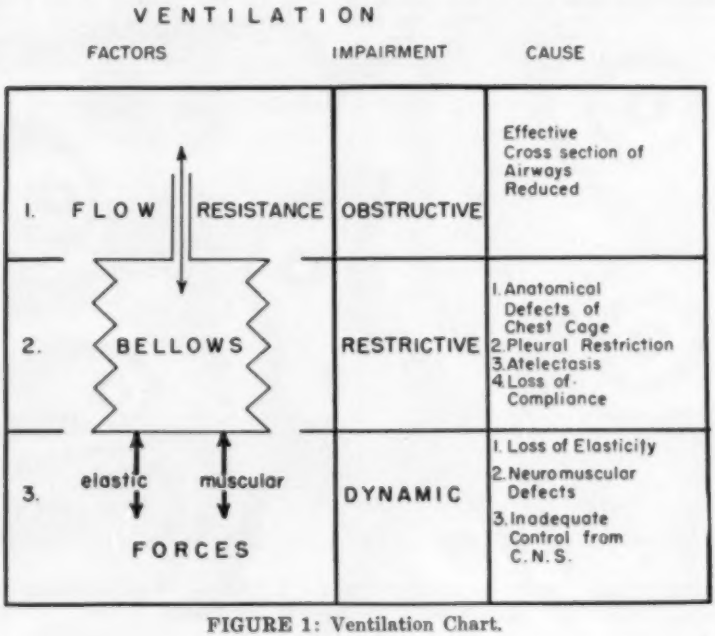

FIGURE 1: Ventilation Chart.

of which hang models of jet airplanes which they have constructed. Each child is a member of the Jet Room Club and his specific therapy is transcribed on the back of his membership card.

Therapeutic Measures

AIDS TO IPPB THERAPY

Climate: The low humidity of the Southwest helps to dry up bronchial secretions, and the lower air density in Albuquerque reduces respiratory work.

General: Adequate diet, proper clothing, prevention of fatigue, avoid-spasm with nebulized bronchodilators, mechanical clearing of the respiratory infections, avoidance of respiratory irritants (dust, smoke, allergenic irritants), and immediate treatment of respiratory infections.

Specific: Expectorants to promote bronchial drainage, relief of bronchospasm with nebulized bronchodilators, mechanical clearing of the respiratory tract by coughing or postural drainage, antihistamines, combination medications (such as Tedral), hormones (ACTH, Cortisone), and suppositories (Aminophylline, Tedral).

ADMINISTRATION OF IPPB TO CHILDREN

Method: The child is seated on a high swivel stool called the "pilot's seat." All positive pressure therapy in older children has been given via the Bennett flow sensitive pressure breathing therapy unit (Model TV-2P)* The pressure gage is set for eight to 10 cm. positive water pressure. A

*Children from ages one to five received therapy via the Bennett Infant Pressure Breathing Therapy Unit, modified from the TV-2P Model to give greater flow sensitivity and less dead space in the connecting and face piece attachments. All Bennett Therapy Units furnished by V. Ray Bennett & Associates, Inc., Los Angeles, Cal.

Apparatus for measuring Functional Residual Capacity and recording Pulmonary Nitrogen Clearance

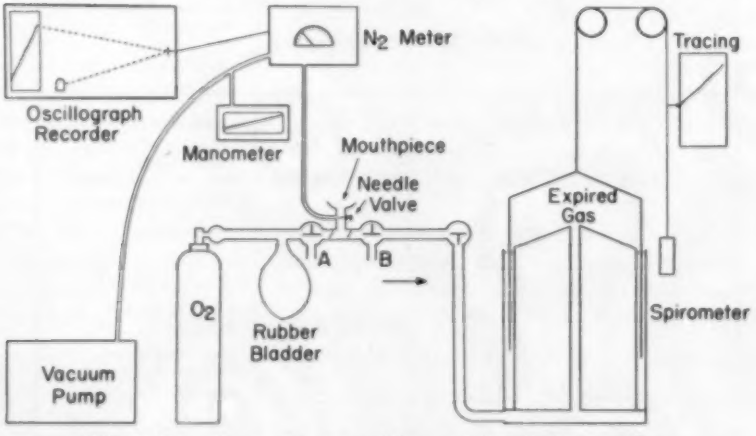

FIGURE 2: Apparatus for mixing and distribution studies.

special sized mask to fit the child is rolled down from the nose and over the mouth to fit snugly. The child is then instructed to breathe deeply, raising the upper chest up to meet the doctor's hand during inspiration, and then to exhale completely until the abdomen or lower chest meets the doctor's other hand. Emphasis is placed on breathing deeply and slowly in order to avoid hyperventilation. (One hundred per cent oxygen is used both for pressure and nebulization). After the child has adjusted to the positive pressure breathing, the aerosol mixture is added to the treatment by adjusting the flow rate to the nebulizer to produce a true aerosol which will be inhaled during the inspiratory phase. The child watches the control pressure and mask pressure dials as they move, and many of the small children make believe they are jet pilots on a mission, flying high up in the skies, breathing in oxygen as many of their Air Force father pilots do. Initial pressures of eight to 10 cm. may eventually be increased to 10 to 15 cm., depending on the age of the child and the severity of his condition. Initial treatments range from five to ten minutes; most routine treatments are of ten minutes duration; occasionally some may be increased to 12 minutes. Frequency of treatments is based on acuteness and severity of the child's respiratory problem. *Status asthmaticus* is usually treated twice daily until significant improvement occurs, as may be bronchiectasis, complicated by acute pneumonitis. Treatments are gradually reduced in number and discontinued when the child's condition so warrants. The mask is held either by the nurse or the older child himself during the entire treatment, and children are encouraged to stop and blow their nose or cough, or get up any secretions loosened up during the treatment.

FIGURE 3: IPPB therapy being administered to five-year old bronchiectasis patient with Bennett Unit.

Following therapy they are instructed to do only moderate activity during the next four-hour period and, in many instances, to engage in postural drainage. Occasionally some older children can aid themselves between treatments by further postural drainage and breathing exercises.

Aerosol Medications: Aerosol medications are of four types: bronchodilators, antibiotics, wetting agents, and digestive enzymes. The most satisfactory bronchodilator in children has been isopropylarterenol (Isuprel 1/200 dilution) hydrochloride**; a racemic epinephrine solution (Vaponefrin) has been used in those initially or eventually non-responsive to Isuprel; Aerolin compound was discontinued because of its oily characteristics and atropine-procaine fractions. Among the antibiotics, Terramycin aerosol has been most generally used, when organisms were shown to be sensitive to the drug (it remains stable when combined with the other aerosol agents); penicillin and streptomycin have been helpful. Alevaire** has been used almost exclusively as a wetting agent to help in the reduction of surface tension, liquefaction and emulsification of mucus, and potentiation of antibiotic agents. The enzymatic agent Tryptar*** has been used sparingly where indicated for the further liquefaction of thick tenacious secretions in children with asthma, bronchiectasis, and cystic fibrosis of the pancreas.

Supportive Therapy: Those children who have definite allergies are desensitized by the administration of weekly, bi-weekly or monthly allergenic extracts (in most cases Hollister-Stier extracts were used). Where respiratory attacks are precipitated by colds, children may also receive cold shots (H. influenzae Serobacterin—Sharp & Dohme).

Psychotherapy has benefited many children whose respiratory or systemic complaints are associated with emotional disturbances. Play therapy in many instances may be continued over many months, as similarly recounted in Baruch's "One Little Boy."[5]

EVALUATION OF THERAPY

The benefits which children derive from IPPB therapy are evaluated subjectively by symptomatic and physical changes. Of prime consideration in symptomatic improvement are changes in appetite, breathing character, cough or wheezing, fatigability, infections, medications required, and sleeping. Physical changes observed are alertness, color, vigor, weight, type and quality of respirations, change in thoracic or other configurations, exercise tolerance, breath sounds, pulse and blood pressure, and temperature.

The change in routine laboratory evaluations—blood count, decrease in bacterial organisms, change in x-ray films of chest and sinuses, and change in allergic sensitivities—offer some objective measures of improvement. The most impressive objective observations come, however, from comparative "before and after therapy" pulmonary function studies.

**Alevaire and Isuprel furnished by Winthrop Laboratories, Inc., New York, N. Y.
***Tryptar Aerosol furnished by Armour Laboratories, Chicago, Ill.

Results

CLINICAL RESULTS

Newborns and Infants—One hundred and seven newborns have been resuscitated employing the Goddard-Bennett-Lovelace Infant Hand Resuscitator, with an average number of treatments ranging from one to 10, and a duration of two to 20 minutes. Eighty-seven of these newborns survived, and if correction is made for extrapulmonary deaths (intracranial bleeding and congenital cardia), the survival rate rises to 90 per cent.[6] Ten infants, ranging from three days to one year of age were treated with IPPB via the GBL Infant Hand Resuscitator for segmental atelectasis, pneumonia, acute laryngo-tracheo-bronchitis, bronchiolitis and various congenital anomalies (tracheo-esophageal fistula, incomplete tracheal rings, etc.). The average number of treatments ranged from two to 10, duration 10 to 15 minutes, with 70 per cent survivals. (One death was in an infant with multiple congenital anomalies, one in a 20 days old infant with tracheo-esophageal fistula and post-operative atelectasis, and the third was in a four months old infant with amyotonia congenita who had recurrent bouts of pneumonitis.)

Children—Ninety children ranging from one to 17 years of age have received IPPB therapy. Eighty-eight, (98 per cent) have improved with therapy. In over 1800 treatments in 100 children ranging in age from a few days to 17 years, and in over 200 treatments in 107 newborns, we have not produced pathological damage from intermittent inspiratory positive pressure breathing. The only ill effects noted have been dizziness and headache, with occasional vomiting, in children who have breathed too rapidly and hyperventilated.

Childhood Asthma—Forty-six children with different degrees of severity of asthma have been treated with IPPB. In each case 0.5 cc. of Isuprel or Vaponefrin was used, diluted in one cc. of distilled water. In cases where indicated other aerosols have been added—0.5 cc. Terramycin for combating infection, 0.5 cc. Alevaire and/or 0.5 cc. Tryptar to liquefy secretions. Ninety-six per cent of these children were helped by IPPB. The significant findings in this series is that the younger the child, the better response he shows to IPPB therapy.[8]

Age Group One to Five Years: Ten children were treated in this age group. One severe case died following an acute anoxic attack, 15 months after IPPB was initiated. Post mortem examination revealed chronic anoxic changes with extensive secondary degenerative changes in the ganglion cells of the cerebral cortex, the spinal cord, the dentate nucleus and olive, and focal degenerative changes of the peripheral nerve bundles. Acute anoxic hemorrhagic areas were present in the brain, heart and lungs. Respiratory pathology revealed mild chronic laryngitis and tracheitis, chronic bronchitis and bronchiolitis, some focal pneumonia, pulmonary emphysema and hypertrophy of the right heart (cor pulmonale). The only other child in the entire group of asthmatics who did not continue to improve with IPPB therapy was a

two-year old boy who took one treatment and refused any more; treatment was discontinued, as his asthma was mild. Two other children in this age group were hospitalized in *status asthmaticus* and have improved to the point of where one weekly treatment suffices to keep them subjectively and objectively free of asthmatic symptoms and signs. The remaining six children in this group range in severity from mild to moderate and may receive treatment once a week, once a month, or only as needed. These children are treated with IPPB in an attempt to: (1) prevent mild chronic or acute anoxia, (2) improve lung and chest compliance and overcome emphysema, (3) and in three cases to supplant ACTH therapy.

Age Group Six to 11 Years: This is the largest group in our asthmatic series. All 29 children in this group, with mild to severe asthma, have shown improvement. There has been improvement in general well-being, in appetite; less wheezing, coughing and sneezing; less fatigability; fewer infections; less medication required; and improvement in sleeping. Many children confined to bed or the home have returned to normal activities and school. Physically, these children are more alert, their color has improved, they have less respiratory difficulty, and little dyspnea, with improvement in exercise tolerance. Some have obvious decrease in anterioposterior chest diameter and emphysematous configuration of the chest, and many have shown substantial weight gains. Objectively, there has been improvement in obstructive, restrictive, and ventilation impairment in 100 per cent of the cases. This response to IPPB therapy in these school age children indicates the likelihood of reversal of pulmonary pathology when long term therapy is carried out. Response to isolated treatment may be of little significance or value.

Age Group 12 to 17 Years: Seven children, three of whom were suffering from severe asthma, showed remarkable improvement. Pulmonary function studies in this age group have been most successful,

TABLE I
CHILDREN RECEIVING INTERMITTENT POSITIVE PRESSURE-AEROSOL THERAPY (SEPTEMBER 1952-JUNE 1955)

Age Group	Number Treated	Average Range of Treatments	Improved with Therapy No.	%	Number Receiving Other Therapy
Newborns Resuscitated	107	1 - 10	87	81	
Infants	10	2 - 10	7	70	4
Children	90		88	98	37
Asthma	46	12 - 75	44	96	26
Bronchiectasis and Bronchitis	10	10 - 50	10	100	4
Chronic Cough	18	6 - 24	18	100	
Cystic Fibrosis of Pancreas	1	46	1	100	1
Sinusitis and Misc. Respiratory Conditions	15	1 - 12	15	100	6

due to the better cooperation from these children and the larger pulmonary volumes which can be more accurately measured. This group not only shows the objective changes seen in adults with emphysema (increased vital capacity, maximal breathing capacity, and instantaneous inspiratory and expiratory flow rate patterns) but also significant changes in residual volume and pulmonary emphysema, with a reversal toward restoration of normal lung volumes.

Chronic Cough—Eighteen children who were first seen for a chief complaint of chronic cough were treated with IPPB, together with an aerosol comprised of a bronchodilator, antibiotic, and distilled water. The duration of the symptoms ranged from six weeks to four years. All previous treatments, including antibiotics, chemotherapeutic agents, allergy diets, antihistaminics, and cough preparations were unsuccessful. The investigative studies revealed no specific cause other than low grade bacterial infection and occasional mild allergic sensitivity. Roentgenograms were usually negative; occasionally there was a questionable increase in the bronchovascular markings of the lungs. Pneumotachographic tracings frequently showed some obstructive impairment, which improved with IPPB therapy. Other pulmonary function tests rarely showed any restrictive or ventilatory impairment. This group of children showed the best results in our entire series. In 100 per cent of the cases, six to 24 10-minute treatments "cured" these children of their coughs, and none have returned except for other non-associated complaints.

Bronchiectasis and Bronchitis—Ten children, four with bronchiectasis and six with chronic bronchitis, have improved with IPPB therapy and aerosols consisting of a bronchodilator, antibiotic, distilled water, and in some cases Alevaire and/or Tryptar. There has been disappearance of cough and fatigue, increased appetite, ability to sleep and increased resistance to infection. Fever has disappeared, color and vigor have returned, with weight gain, clearing of the chest, and increase in exercise tolerance.

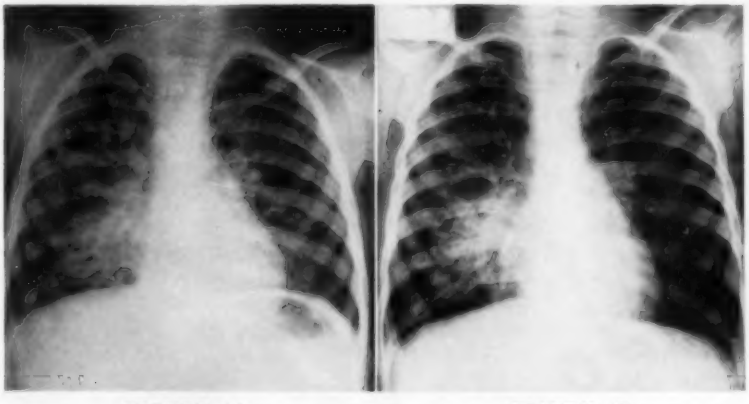

FIGURE 4A FIGURE 4B

Figure 4: X-rays of three-year old girl with cystic fibrosis of pancreas. (A) Before IPPB started. (B) After 46 treatments over an eight-month period.

X-ray films have shown improvement (both chest and sinuses); pneumotachographic tracings have shown decrease in obstructive impairment; other tests have shown an increase in the tidal volume, with a more even intrapulmonary mixing.

Cystic Fibrosis of the Pancreas—Only one case of cystic fibrosis of the pancreas has been treated with IPPB therapy. We believe the results in this case warrant its publication. This three-year old girl had been admitted to hospitals four times in the nine months prior to initiation of her IPPB therapy. The main finding on all four occasions had been bronchopneumonia and, on two occasions, atelectasis of the right middle lobe. IPPB therapy was started via the Bennett Infant Therapy Unit, using 1.5 cc. Tryptar aerosol (62.5 thousand units), 0.5 cc. Terramycin (75 mgm.), 0.5 cc. Alevaire, 0.5 cc. Isuprel and 0.5 cc. distilled water. She was treated daily for 10 days, during which time three treatments incorporated Tryptar aerosol. Following discharge from the hospital she has been treated in the outpatient department, first, three times weekly, then twice weekly, and now once weekly. In addition to IPPB therapy, she is on a cystic diet with daily pancreatin and erythrocin. Clinically, her cough has lessened, fever has disappeared, she has gained eight pounds, has fewer colds, and even less foul, bulky stools. Her x-ray films have shown some clearing of the typical "snowflake" shadows superimposed on chronic bronchitis and pneumonia of the right hilum and right lower lobe, although some shadows and increased bronchovascular markings remain (Fig. 4). Her pneumotachographic tracings have shown improvement in her obstructive-restrictive impairment.

Sinusitis and Miscellaneous Respiratory Conditions—Seven patients with sinusitis alone benefited from two to six IPPB treatments. Four children with sinusitis and allergic rhinitis have benefited from four to 10 treatments. In all 11 of these cases a bronchodilator-water aerosol mixture was employed, and in five an antibiotic. In the four with allergic rhinitis, allergenic extracts have now supplanted IPPB therapy. Four additional children with other respiratory problems have been treated with IPPB therapy alone or together with an aerosol. The left lung of a two-year old child with post-operative atelectasis was expanded by IPPB-aerosol therapy; tracheotomy in a two-year old with severe croup was circumvented by means of IPPB-aerosol therapy; a three-year old child with bulbar polio was aided by IPPB therapy; and a six-year old boy with triple fractures of the skull and bleeding at the base of the brain, with pressure on the cardio-respiratory center, was maintained over a two-hour period, using the GBL Infant Resuscitator with a large hand bulb, until a neurosurgeon operated and decreased the intracranial bleeding (10 cm. positive pressure).[3]

LABORATORY RESULTS

The clinical and subjective signs of improvement have been gratifying in our studies. The unequivocal objective results, however, have come from studies done before and after a single treatment, or before therapy

was initiated and after an appreciable period of therapy to show significant improvement.

Pneumotachographs—From these tracings, changes in not only the airflow but all three types of ventilatory impairment (obstructive, restrictive and dynamic) can be studied. The upper tracing in Fig. 5 shows the poor respiratory function of six-year old JS, whose asthma started at the age of two years. The usual asthmatic agents, plus ACTH, and even IPPB with a bronchodilator aerosol were unsuccessful in controlling his severe attacks. Finally, with the incorporation of Tryptar and Alevaire into the aerosol being administered by IPPB, he has made a good response and is attending school regularly. His pneumotachographic tracing before IPPB-Tryptar-Alevaire aerosol therapy was started shows: obstructive impairment evidenced by (a) shallow inspiration and (b) long exhalation time (1.8 second) ; restrictive and dynamic impairment with (c) prolonged time interval from the peak inspiratory flow to the peak expiratory flow (1.8 second). Following ten treatments, obstruction lessened considerably, as denoted by a more regular respiratory rhythm with (a′) increase in the amplitude of both the inspiratory and expiratory phases and (b′) decrease in the exhalation time (0.7 second). Dynamic and restrictive impairment show some improvement as evidenced by the now (c′) fairly normal time interval between the peak inspiratory and peak expiratory flows (1.1 second).

Pulmonary Function Tests—While pneumotachographs serve as a rapid screening procedure of ventilatory function, and offer a psychological boost to the patient and parent, our most accurate determinations have come from our other pulmonary function studies.

Obstructive impairment in children is best analyzed from the timed vital capacity, since many children with severe pulmonary disease are unable to exert maximum breathing effort to give a maximum breathing capacity evaluation. The first second vital capacity is the most important, since a three second value may sometimes not be obtained. In the spirogram record (Fig. 6) of a 12-year old boy with asthma, marked

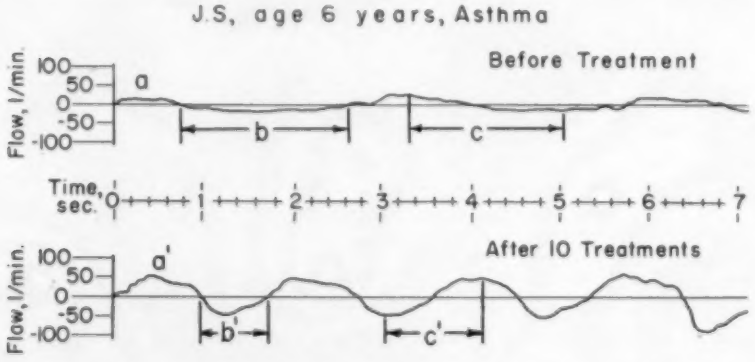

FIGURE 5: Pneumotachograph of six-year old boy with asthma.

obstruction is present, as denoted from a first second timed vital capacity of 52 and a three second timed vital capacity of 86. (His tidal volume, inspiratory capacity, expiratory reserve and vital capacity are within normal range for his age and height).

The vital capacity and residual capacity offer good indices of restrictive impairment, and the residual capacity gives further evidence of the presence of emphysema, which is frequently associated with a loss of compliance and elasticity. Mixing and distribution impairment, we believe, is best studied by measuring the respiratory volume required to accomplish clearance of an inert gas (nitrogen) from the lungs while breathing oxygen. From these measurements we can then classify the degree of pulmonary function impairment from both a volumetric and a functional basis.

TABLE II
VOLUMETRIC AND FUNCTIONAL STANDARDS FOR PULMONARY FUNCTION IMPAIRMENT

Type of Pulmonary Impairment	Measurement	Degree of Pulmonary Function Impairment				
		Normal	Slight	Moderate	Advanced	Extreme
Volumetric: (Emphysema)[7]	RV/TC	.25 & —	.25—.35	.35—.45	.45—.55	.55 & +
Functional: (Ventilatory inefficiency)[6]	N_2 Clearance Equivalent	15 & —	15—20	20—25	25—30	30 & +

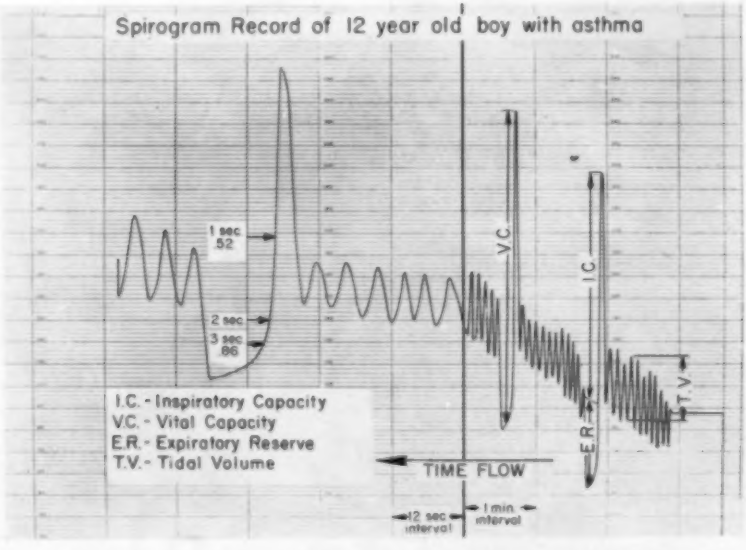

FIGURE 6: Spirogram record of 12-year old boy with asthma.

In Table III we have analyzed the obstructive, restrictive, and mixing and distribution impairment and their changes after therapy in three different age groups of asthmatic patients. JS, age six years, (whose pneumotachographs appear in Fig. 5) has improved from an advanced degree of pulmonary function impairment to a moderate degree, after 10 IPPB treatments. There has been an increase in his vital capacity with an accompanying increase in his residual volume to normal for his age, sex, and height. Obstructive impairment has improved, with a 15 per cent increase in the first second timed vital capacity, and his improved nitrogen clearance demonstrates better mixing and distribution. RF, age nine years, suffering from mild asthma for six years, has shown slight improvement

TABLE III
EXAMPLES CHARACTERISTIC OF PULMONARY FUNCTION IMPAIRMENT IN THREE AGE GROUPS OF ASTHMATIC CHILDREN

					Obstructive		Restrictive		Pulmonary Function Evaluation			
Pt.	Sex	Age	Test	Total Capacity (Liters)	Timed Vital Capacity 1 sec.	3 sec.	Vital Cap. (Liters)	Resid. Cap.	Mixing and Distribution N_2 Clearance Ventilation	Volumetric RV/TC	Functional N_2 Clearance Equipment	Correlation*
JS	M	6	1	1.72	75	—	1.49 (77 per cent of predicted)**	0.23	23.3	.13	26.9	Volume Relationship: Normal
			2	1.95	90	97	1.60 (83 per cent of predicted)	0.35	16.2	.18	20.2	Function Impairment: Improved from advanced to moderate
RF	M	9	1	3.07	68	92	2.30 (104 per cent of predicted)	0.86	25.2	.25	18.5	Volume Relationship: Normal
			2	3.01	72	98	2.31 (104 per cent of predicted)	0.78	23.3	.23	19.0	Function Impairment: Slight
GE	F	17	1	4.31	56	83	2.15 (59 per cent of predicted)	2.32	64.6	.50	21.5	Volume Relationship: Improved from advanced to slight
			2	4.03	61	90	2.86 (79 per cent of predicted)	1.17	48.8	.29	22.7	Function Impairment: Slight

*Correlation is the agreement between volumetric and functional methods of evaluation of degree of Pulmonary Function Impairment.
**Vital Capacity.

in his timed vital capacity and his obstructive impairment, with a slight decrease in his residual volume and emphysema.

GE, age 17 years, demonstrates reversibility in all types of pulmonary function impairment. She had eczema as an infant, with wheezing from the age of two years. The usual asthmatic agents, plus vitamins and cortisone, failed to control her asthma. She was admitted to the hospital in *status asthmaticus*, and IPPB therapy employing an aerosol mixture of Isuprel-Alevaire-Tryptar-water was given initially twice daily, then daily. She was discharged home 10 days later to continue IPPB therapy at home. In six months she had gained weight and returned to normal activities, with a decrease in the number and severity of her attacks. Her x-ray films showed clearing of the sinuses, with some decrease in the bronchovascular lung markings; her pneumotachographs showed considerable decrease in obstructive and restrictive impairment. From Table III and Fig. 7, changes in her pulmonary function show less obstruction, evidenced by an increase in timed vital capacity. The residual volume has decreased by 50 per cent to approximately the estimated normal value, with a corresponding 33 per cent increase in vital capacity. Her degree of pulmonary function impairment, based on the volumetric RV/TC ratio, has changed from advanced to slight. Her nitrogen clearance ventilation has decreased 25 per cent due to improvement in her functional residual capacity.

The Place of IPPB Therapy in Pediatrics

IPPB, with high positive pressures given over short, safe time intervals, is successful in the resuscitation of newborns. In 70 per cent of infants IPPB-aerosol therapy has been beneficial, and in 98 per cent of children from one to 17 years of age it has improved their respiratory condition. In childhood asthma not only has IPPB provided relief and control of symptoms and arrested the progress of the disease but it has reversed the chronic changes due to edema, bronchospasm and emphysema, and promoted the restoration of normal lung compliance and elasticity. We

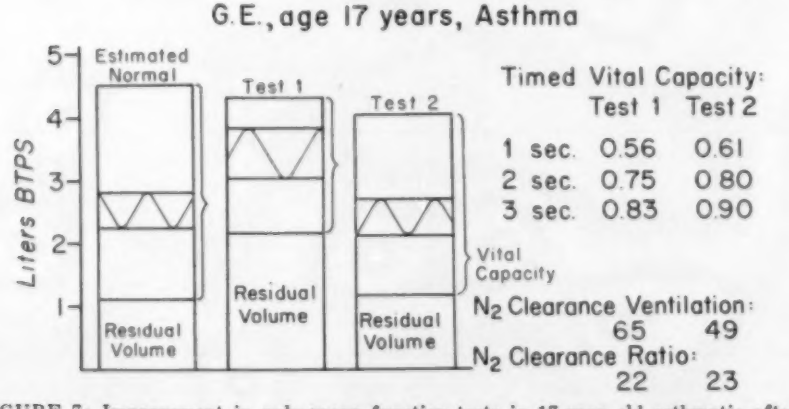

FIGURE 7: Improvement in pulmonary function tests in 17-year old asthmatic after six months IPPB therapy.

believe chronic cough, chronic bronchitis and bronchiectasis are probably all progressive stages of the same "end" respiratory disease process. The first is cured with minimal IPPB therapy; bronchitis is helped with more intensive therapy, while bronchiectasis requires a long-term approach. With the dispersion of aerosol to all parts of the respiratory system in IPPB therapy, it is proving not only effective in alleviating symptoms and physical signs in these conditions, but playing a larger role in prophylaxis. While IPPB-aerosol therapy in cystic fibrosis of the pancreas does not correct the basic enzymatic deficiency, it protects against the recurrence of atelectasis so commonly seen in these children, holds down infection, and makes for a more normal lung compliance and elasticity—thus being not only active treatment, but prophylaxis against further infection and chronic lung changes. In sinusitis and miscellaneous respiratory conditions IPPB offers a more rapid, effective means of therapy. Therefore, in the respiratory conditions of children herein treated and reported on, IPPB-aerosol treatment has offered an adjunctive method of therapy in some, a "cure" in others, and prophylaxis against further infection and the development of chronic pulmonary pathology in others. Continued observation of these children over a long follow-up period will substantiate these conclusions.

Our studies have been limited to the application of intermittent positive pressure in the inspiratory phase. Expiratory positive or negative pressures have not been applied because of the labored effort required in this type of therapy, and the desire to hold at a minimum the respiratory work required of many of these small children with severe pulmonary involvement. Bronchodilators alone or IPPB alone were not studied, as we believe sufficient evidence has been presented by Segal, et al.[8] to show the superiority of the combination of IPPB with bronchodilator agents. We believe the addition of a wetting agent enhances the liquefaction of sputum and potentiates the action of antibiotic aerosols. Tryptar, when used sparingly and only when necessary, due to its irritative qualities,[9] has made the difference in success or failure in several of our chronic cases. The use of antibiotic aerosols has been beneficial in cases with chronic infection—sinusitis, bronchiectasis, and cystic fibrosis of the pancreas. We have not studied the diethylaminoethyl ester of penicillin advocated by Barach, et al.[10] or have we been able to induce deliberate coughing in the younger age groups. Coughing chamber methods have not been studied, due to their impractical use in children. The use of supportive measures has been helpful in desensitizing children against allergies and upper respiratory infections. Short intensive courses of ACTH and cortisone allow remissions without the risk of adverse reactions. Psychotherapy plays an important role in many of these children.

The optimal method of use of IPPB in children seems to be an initial concentrated effort of one to two treatments daily, followed by two to three times a week treatments, and then weekly treatments until improvement or "cure" warrants discontinuance of therapy. In many asthmatics and children with chronic respiratory conditions long term therapy on a weekly or occasional "booster" type program is advocated. Children

must be instructed to breathe deeply and slowly and avoid hyperventilation which may cause headache, dizziness and vomiting. No case has been studied in which there is a contra-indication to the use of IPPB-aerosol therapy in children, nor has there been any pathological damage seen due to the use of positive pressure.

SUMMARY

1. A method for the use in pediatrics of intermittent positive pressure breathing (IPPB) therapy with supplementary use of bronchodilator drugs, antibiotic drugs, a wetting agent, and an enzymatic agent has been discussed.

2. A plan of investigation for studies in children to determine the effectiveness of such therapy is reviewed.

3. A ventilation chart has been proposed to simplify the factor-impairment-cause relationship of pulmonary function.

4. An accurate evaluation of the degree of pulmonary function impairment in children has been made from the following physiological tests: pneumotachographs, timed vital capacity, residual capacity, RC/TC $\frac{\text{(residual capacity)}}{\text{(total lung capacity)}}$ ratio, and the nitrogen clearance equivalent.

5. It has been shown that IPPB-aerosol therapy in pediatrics has proved to be an adjunctive, a curative, and a prophylactic type of treatment in children with asthma, chronic coughs, bronchiectasis and bronchitis, cystic fibrosis of the pancreas, sinusitis and miscellaneous respiratory conditions.

6. Significant reversible changes, not heretofore seen in IPPB therapy in adults, have been noted in some children with chronic emphysema, with as much as 50 per cent decrease in the residual volume, 33 per cent increase in vital capacity, and 25 per cent decrease in nitrogen clearance ventilation.

RESUMEN

1. Se discute un método para usar en pediatría la presión positiva intermitente (IPPB) con el uso suplementario de drogas broncodilatadoras, antibióticos, un agente humedecedor, y un agente enzimático.

2. Se revisa un plan de investigación para determinar en los niños la efectividad del método.

3. Se propone una gráfica de ventilación para simplificar el factor de deficiencia como causa en relación con la función pulmonar.

4. Una valuación exacta del grado de deficiencia de la función pulmonar en los niños se ha hecho mediante las pruebas siguientes: (a) neumotacografías, capacidad vital en relación al tiempo, capacidad residual, RC/TC $\frac{\text{(Capacidad residual)}}{\text{(Capacidad pulmonar total)}}$ y el equivalente de liberación de nitrógeno.

5. Se ha demostrado que el tratamiento por IPPB es un adjunto, curativo y profiláctico en el tratamiento de los niños con asma, tos crónica

bronquiectasia, bronquitis, fibrosis cística del páncreas, sinusitis otras variadas afecciones respiratorias.

6. Se han notado en los niños algunos cambios reversibles significativos que hasta ahora no han observado en los adultos mediante el IPPB, en casos de enfisema crónico, con tanto como 50 por ciento de decrecimiento del volumen residual, 33 por ciento de aumento de la capacidad vital, y 25 por ciento de disminución de la liberación de nitrógeno.

RESUME

1. L'auteur discute une méthode qui permet l'utilisation en pédiatrie du traitement par la respiration sous pression positive intermittente, avec usage associé de produits bronchodilatateurs, d'antibiotiques, d'un agent humidifiant, ou d'un agent enzymatique.

2. L'auteur developpe un programme de recherches pour étudier chez les enfants le moyen de déterminer l'efficacité d'un tel traitement.

3. L'auteur propose un graphique de ventilation pour simplifier le rapport élément-troubles de la fonction pulmonaire.

4. Une estimation précise du degré du trouble de la fonction pulmonaire chez les enfants a été faite d'après les tests physiologiques suivants: pneumotachographies, mesure du volume expiratoire maximum en un temps donné, de la capacité residuelle, du rapport $\frac{\text{(capacité-résiduelle)}}{\text{(capacité pulmonaire totale)}}$ et étude de l'élimination de l'azote.

5. Il a été démontré que le traitement par aérosols par la respiration sous pression positive intermittente en pédiâtrie était un traitement du type adjuvant, curatif et prophylactique chez les enfants atteints d'asthme, de toux chronique, de bronchiectasie et de bronchite, de fibrose kystique du pancréas, de sinusite et de différents états respiratoires.

6. Des modifications réversibles significatives, qui n'étaient pas visibles auparavant dans le traitement par la respiration sous pression positive intermittente chez les adultes, ont été notées chez quelques enfants atteints d'emphysème chronique avec des chiffres tels qu'une diminution de 50% du volume de l'air résiduel, une augmentation de 33% de la capacité vitale, et une diminution de 25% du coefficient d'élimination de l'azote.

ZUSAMMENFASSUNG

1. Es wird eine Methode erörtert, die die Anwendung intermittierender Überdruckatmung in der Kinderklinik unter zusätzlicher Benutzung bronchodilatatorischer und antibiotischer Medikamente sowie eines Befeuchtungsmittels und eines Enzympräparates zum Gegenstand hat.

2. Ein Untersuchungsplan zum Studium der Wirksamkeit solcher Therapie bei Kindern wird dargelegt.

3. Eine Ventilationstabelle wurde vorgeschlagen, um die Ursachen ungenügender Lungenfunktion zu differenzieren.

4. Eine genaue Beurteilung des Minderungsgrundes der Lungenfunktion bei Kindern wurde aus folgenden physiologischen Tests gewonnen: Pneu-

motachogramm, Atemstoss, Residualkapazität, Verhältnis Residualkapazität: Totalkapazität und Stickstoff-Clearance-Äquivalent.

5. Es wurde gezeigt, dass intermittierende Überdruckatmung mit Aerosol in der Kinderheilkunde sich als zusätzliche Heil- und prophylaktische Behandlung bei kindlichem Asthma, chronischem Husten, Bronchiektasen und Bronchitis, zystischer Fibrose des Pankreas, Sinusitis und verschiedenen Veränderungen des Respirationstraktes bewährt hat.

6. Deutliche reversible Veränderungen, die bei der intermittierenden Überdruckatmung bei Erwachsenen bisher nicht gesehen werden konnten, wurden bei einigen Kindern mit chronischem Emphysem beobachtet mit Verminderung der Residualluft bis um 50%, Vergrösserung der Vitalkapazität bis um 33% und einer Herabsetzung der Stickstoff-Clearance bis um 25%.

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Abnormal Ventilatory Patterns in Mitral Stenosis

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Introduction

Although the genesis of the respiratory abnormality in mitral stenosis has not been completely explained, the assumption is usually made that a relationship exists between increasing pulmonary artery pressure and the severity of respiratory defect. The implication, then, is that this abnormality is a purely mechanical one, and thus dependent on the degree of stenosis at the mitral valve. Such an assumption does not take into consideration such complications as varying degrees of rheumatic myocarditis or rheumatic pneumonitis, occurring during the development of mitral stenosis. If circulatory measurements, particularly of the mean pulmonary artery pressure, can be shown to have a clear-cut correlation with measurements of pulmonary function, the evidence would indeed favor a purely mechanical factor as the chief cause of the respiratory abnormality. In the present study pulmonary and circulatory measurements have been compared in a group of patients with mitral stenosis in an effort to clarify the nature of the respiratory defect involved.

Material and Methods

Sixty-one patients with pure mitral stenosis were randomly selected for study. Cardiac catheterization provided measurements of cardiac output, pulmonary artery pressure, pulmonary capillary pressure, and arterial oxygen content and saturation by methods previously reported by Cosby et al.[1] Inspiratory reserve, tidal volume, and expiratory reserve were determined by closed spirometry, in the sitting position, and were converted to BTPS (body temperature, ambient pressure, saturated). Maximum breathing capacities and timed vital capacities were performed according to the method of Motley.[2] Oxygen consumption and the volume of oxygen consumed per litre of ventilation were determined by collection of three-minute samples in a Douglas bag; the partial pressures of oxygen and carbon dioxide were measured by an infrared carbon dioxide analyzer and the Pauling oxygen analyzer. Five patients were studied both before and several months after mitral commissurotomy. Three others were studied from a respiratory standpoint by the methods of Riley.[3]

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TABLE I
CARDIORESPIRATORY DATA ON 61 PATIENTS WITH PURE MITRAL STENOSIS

	I-15 Patients			II-15 Patients			III-15 Patients			IV-16 Patients		
Groups	Mean	Range	S.D.[1]	Mean	Range	S.D.	Mean	Range	S.D.	Mean	Range	S.D.
Mean M.P.A.,[2] mm. Hg.	76.8	93-62	10.4	52.8	60-46	4.6	39.7	44-35	3.6	25.6	34-17	5.4
Cardiac Output, L/Min.	3.00	4.4-1.3	0.93	3.76	6.0-1.6	1.30	4.37	7.8-1.8	1.98	3.79	6.8-2.2	1.32
Cardiac Index, L/Min.	1.85	3.0-1.0	0.58	2.32	3.5-1.1	0.76	2.77	4.7-1.2	1.26	2.35	4.1-1.3	0.79
Pulm. Art. Resistance[3]	28.2	56.2-16.3	10.7	16.0	31.9-8.3	6.50	11.0	19.4-5.0	4.80	7.60	12.5-3.5	3.08
O_2 Cons., cc/ Sq. M.[4]	186	285-113	54.6	201	329-105	61.0	210	340-100	77.0	172	277-118	34.0
Art. O_2 Sat. %[5]	89.3	100-75.0	6.73	94.0	100-84.4	5.40	96.4	100-85.0	5.80	94.6	100-86.1	4.91
Vital Cap., cc.	2442	3600-1200	752	2326	3400-780	769	2693	4200-720	966	3000	4320-2000	820
Vital Cap., % Predicted	63.2	97-39	19.0	67.3	95-22	20.1	68.3	90-22	23.2	83.0	100-66	9.80
Max. Breathing Cap., Litres	61.3	89.6-32.3	19.5	57.4	86.7-13.4	19.3	59.5	108.8-15.4	25.7	71.5	144-36.8	31.2
Max. Breathing Cap. % Predicted	64.8	100-39.5	18.5	64.2	100-17.1	24.1	63.3	99-20.3	21.8	71.8	100-42.3	14.7
Inspiratory Reserve, cc.	776	1200-320	309	1048	2000-200	474	1017	1960-240	604	1109	1520-480	303
Expiratory Reserve, cc.	996	2000-200	495	830	1920-434	422	913	1600-320	367	1305	2720-640	746
O_2 Consumed/ L. Vent., cc.[6]	30.6	37.5-19.8	5.40	34.2	40.0-26.3	4.90	33.1	40.8-22.6	5.10	32.8	43.5-19.0	6.90

[1] S.D.—Standard deviation.
[2] M.P.A.—Mean pulmonary artery pressure.
[3] Pulm. Art. Resistance—Pulmonary Artery Resistance in arbitrary units.
[4] O_2 Cons.—Oxygen consumption, cc./ square meter body surface.
[5] Art. O_2 Sat.—Arterial oxygen saturation.
[6] O_2 Consumed—Oxygen consumed per litre ventilation in cc.

Results

The 61 patients with pure mitral stenosis have been divided into four groups according to their level of mean pulmonary artery pressure (see Table I). Those with the highest mean pulmonary artery pressury (Group I) either were in heart failure at the time of examination or gave a history of heart failure in the past. In all the groups except Group IV (q. v. infra) the data followed an expected pattern. With decreasing pulmonary artery pressure in Groups I, II, and III, there was a gradual increase in cardiac output, a decrease in pulmonary vascular resistance, and a rise in arterial oxygen saturation. Group I was the only group in which the mean arterial oxygen saturation fell below 90 per cent.

The mean vital capacity was below normal in every group, Group II being the lowest, and the mean maximum breathing capacity was low in Groups I, II, and III; it returned to a normal level in Group IV. However, 30 per cent of all patients had maximum breathing capacities below 50 litres per minute, which is definitely below the lowest normal limit. The standard deviations of both vital capacity and maximum breathing capacity means were unusually large in all groups.

Although in Groups I, II, and III the cardiac output increased as pulmonary artery pressure decreased, Group IV patients, with the lowest pulmonary artery pressures, had cardiac outputs lower than those of Group III, being comparable to those of Group II. Moreover, the oxygen consumptions of patients in Group IV were lower than in any other group. On the other hand, the respiratory data in Group IV showed a striking improvement over the pulmonary volumina in the other groups. The mean vital capacity, maximum breathing capacity, expiratory reserve and tidal volume showed about a 50 per cent increase over the comparable means in Group III, a difference which was statistically significant (P less than .01).

Table II shows the relationship between the degree of dyspnea and mean pulmonary artery pressure, vital capacity, maximum breathing capacity and arterial saturation. A closer relationship to the degree of dyspnea was evident with mean pulmonary artery pressure and vital ca-

TABLE II

CORRELATION OF DEGREE OF DYSPNEA WITH VITAL CAPACITY, MAXIMUM BREATHING CAPACITY, MEAN PULMONARY ARTERY PRESSURE AND ARTERIAL OXYGEN SATURATION

Dyspnea Graded	No. Patients	Mean Vital Capacity, Per Cent	Mean Maximum Breathing Capacity, Per Cent Predicted	Mean Pulmonary Artery Pressure	Mean Arterial Sat., Per Cent
1	5	81.4	72.2	23.0	92.6
2	17	81.8	75.5	38.3	94.4
3	21	67.6	60.8	60.1	92.2
4	16	60.2	62.1	51.2	93.6

pacity than with maximum breathing capacity. In this series no relationship whatever was present between degree of dyspnea and degree of arterial saturation.

For the entire series of 61 patients, correlation coefficients of mean pulmonary artery pressure with vital capacity, maximum breathing capacity, oxygen consumed per litre of ventilation and arterial oxygen saturation were calculated, as well as the coefficients of arterial saturation, pulmonary vascular resistance and cardiac index with vital capacity and maximum breathing capacity. Only three of these correlation coefficients showed even a borderline significance. Vital capacity versus mean pulmonary artery pressure (r-.430), and vital capacity versus pulmonary vascular resistance (r-.493) were significant at the 1 per cent level. Mean pulmonary artery pressure versus arterial saturation (r-.397) was significant at the 5 per cent level. Because of the large standard deviations of these coefficients, particularly in the pulmonary function measurements, they have little practical significance.

Measurements both before and after mitral valvulotomy were obtainable in only five of the 61 patients. In two of the five cases there were no postoperative changes in either the mean pulmonary artery pressure or the maximum breathing capacity. In the three others a moderate fall in pulmonary artery pressure was accompanied by a parallel increase in maximum breathing capacity.

Three other patients of the original group were studied in greater detail by the methods of Riley and Motley (see Table III). The first, aged 50, with moderate dyspnea on exertion, had a mean pulmonary artery pressure of 49 mm. Hg. The alveolar-arterial gradient, per cent venous

TABLE III

SPECIAL STUDIES ON THREE SELECTED PATIENTS WITH PURE MITRAL STENOSIS

Case No. Age Sex	I 50 Female	II 40 Female	III 54 Female
Art. Oxygen Sat., %	97.1	98.3	83.1
Art. Oxygen Tension, mm. Hg.	105	112	50
Alveolar-arterial Gradient	7	3	59.3
Oxygen Diffusing Capacity	7	8	8.4
% Venous Admixture	5	3	2.7
Ratio Residual Air to Total Capacity	43.3	37.6	61.0
Ratio Dead Space to Tidal Vol.	53.0	54.0	58.0
Mean Pulmonary Artery Pressure	49	55	37*
Maximum Breathing Capacity, % Predicted Value	56.0	82.7	37.2

*Cardiac catheterization performed at later date than these respiratory measurements.

admixture, and oxygen diffusing capacity were normal, but the ratio of dead space to tidal volume was markedly increased. The second, aged 40, with similar symptoms, had an exactly similar respiratory pattern, except for a decrease in the oxygen diffusing capacity, of mild degree, on breathing 14 per cent oxygen. The third, aged 54, had recently recovered from an episode of pulmonary edema. The alveolar-arterial gradient was markedly widened, the per cent venous admixture was markedly increased, and the oxygen diffusing capacity was somewhat below normal. Studies performed after two week's time but not recorded in Table III showed a return of the alveolar-arterial gradient and per cent venous mixture to nearly normal values. In each of the three patients the ratio of residual air to total capacity was increased.

Discussion

In the four groups studied, no striking correlation appeared between cardiac defect and respiratory abnormality, the closest correlation being an inverse one between vital capacity and mean pulmonary artery pressure. Maximum breathing capacity correlated poorly with mean pulmonary artery pressure. This may have been because many of these patients were on prolonged bed rest and thus muscular fatigue probably introduced a variable independent factor in the reduction of maximum breathing capacity.

Patients in Group IV departed from the pattern of the other groups. Although the pulmonary artery pressure was lowest in this group, the trend of decreasing cardiac output with increasing pulmonary artery pressure was reversed, and the cardiac output was lower than in Group III. In respect to respiratory measurements also, Group IV was anomalous. Similar values were obtained in Groups I, II, and III, while in Group IV the measurements increased significantly. Several in Group IV developed acute rheumatic fever following mitral commissurotomy. It is believed that they may represent an important subdivision of mitral valve disease in whom subclinical left ventricular failure was responsible for the circulatory abnormalities present. Patients of this type have been described recently by Ferrer et al.[4]

Confirming Lewis and coworkers[5] and Ellis and others,[6] a closer relationship was established between degree of dyspnea and mean pulmonary artery pressure and vital capacity than between dyspnea and maximum breathing capacity. A close correlation between degree of dyspnea and a reduction in vital capacity is a characteristic of restrictive ventilatory insufficiency, according to Gaensler,[7] in a recent review. Frank et al.[8] commented on the lack of correlation between severe dyspnea and maximum breathing capacity, as well as on the lack of correlation of all ventilatory measurements with the degree of dyspnea. Ellis and coworkers[6] emphasized the lack of correlation between arterial desaturation and degree of dyspnea. In our series no relationship whatever was established between these two parameters. In Ellis' series 8 patients with arterial saturation below 90 per cent all had severe dyspnea, but many severely dyspneic patients had perfectly normal arterial saturation. It seems likely that in such

a group a large proportion would be in acute or chronic pulmonary edema. This was the case in our series.

Such conflicting information about the relation of degree of dyspnea to certain pulmonary function tests led Fowler et al.[9] and Carroll and his co-authors[10] to more detailed analyses of pulmonary function. Of the 13 patients studied by Fowler et al.,[9] five showed an increase in per cent venous admixture, and six showed an increase in respiratory dead space (abnormalities of distribution of blood and gases). There appeared to be no relationship between these parameters and the height of pulmonary artery pressure. But in five subjects showing a decrease in oxygen diffusing capacity, four were dyspneic and had high pulmonary artery pressures. The work of Carroll et al.,[10] on the other hand, showed a partially different pattern. In their group, only a portion of whom underwent cardiac catheterization, patients were dyspneic at a lower level of pulmonary artery pressure. In such patients abnormalities of either diffusion or distribution were present, but not both in any one patient. Conversely, in any patients with high pulmonary artery pressures, abnormalities of both distribution and diffusion were present.

The three patients in our series studied by methods similar to those of Fowler et al.[9] and Carroll and coworkers,[10] reported in Table III, illustrate the marked variability in respiratory data possible at relatively similar levels of pulmonary artery pressure. In addition, the third patient illustrates the significant changes which may occur in a short duration of time after the clearing of acute pulmonary edema.

It would be premature, in the present state of our knowledge of the lungs in mitral stenosis, to attempt an interpretation of the available data. Only two abnormalities of respiratory function have been defined, the decrease in pulmonary volumina exemplified by a progressive decrease in vital capacity, and the marked desaturation of arterial blood found in pulmonary edema. The former appears to be related to the development of pulmonary hypertension and pulmonary arteriosclerosis, and the latter to the development of extreme levels of pulmonary venous pressure found in pulmonary edema. The pathologic features of the lung resulting in abnormalities of distribution and diffusion have not thus far been clearly defined. Prolonged elevation of pulmonary edema, pulmonary arteriosclerosis and arteriolarsclerosis, prior rheumatic pneumonitis, pleural effusion, cardiac and auricular hypertrophy, incipient left ventricular failure and pulmonary thrombi may all play a part in the development of defects in distribution or diffusion. It would seem logical to suppose that abnormalities in diffusion should be related to the thickness and permeability of the alveolar-capillary membrane and thus depend upon the degree and duration of elevation of pulmonary venous pressure. If this supposition is correct, and the data of Fowler et al.[9] are examined in such a light one would conclude that only after prolonged marked elevation of pulmonary venous and arterial pressure does an appreciable abnormality in diffusion develop. The effect of acute pulmonary edema in reducing the oxygen diffusing capacity of the lung has not received sufficient study.

The marked improvement in arterial saturation and oxygen diffusing capacity in Case III in our series, with minimal changes in symptomatology, illustrates the profound and prolonged respiratory defect produced by pulmonary edema.

Abnormalities of distribution could arise from any of the protean manifestations of the rheumatic process; cardiac, pulmonary or pleural. Success in the correlation of abnormal pulmonary function and abnormal pathology may come slowly even with the generous use of lung biopsies in the clarification of the role of each of the cardio-pulmonary abnormalities in the rheumatic state.

SUMMARY

1. Cardiac and respiratory studies have been reported in 61 patients with pure mitral stenosis.

2. The 61 patients were classified into four groups according to the level of mean pulmonary artery pressure. Respiratory measurements varied widely in relation to pulmonary artery pressure. Vital capacity showed the closest correlation with pulmonary artery pressure and resistance.

3. Patients with low pulmonary artery pressures fell into two categories; those with minimal mitral stenosis and those with subclinical left ventricular failure. In both subdivisions of this group, pulmonary function tests were almost within the normal predicted limits for size and age.

4. The degree of dyspnea showed a closer relation to the height of pulmonary artery pressure and to vital capacity than to maximum breathing capacity, and was not related to arterial oxygen saturation.

5. In five patients studied before and after mitral commissurotomy, three showed a reduction in pulmonary artery pressure and a corresponding increase in maximum breathing capacity.

6. The significance of abnormalities of distribution and diffusion has been discussed with three illustrative cases.

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RESUMEN

1. Se relatan los estudios cardio-respiratorios en 61 enfermos con estenosis mitral pura.

2. Se clasificaron los 61 enfermos en 4 grupos de cuerdo con el nivel medio de la presión pulmonar. La capacidad vital mostró la más estrecha relación con la presión pulmonar y la resistencia.

3. Los enfermos con baja presión arterial pulmonar entraron en dos categorías: los que tenían estenosis mitral mínima y los que tenían insuficiencia ventricular izquierda subclínica. En ambas subdivisiones del grupo las pruebas funcionales pulmonares estaban casi dentro de la normal esperado en lo referente a estatura y edad.

4. El grado de disnea mostró una relación más estrecha con la elevación de la presión de la arteria pulmonar y con la capacidad vital que con la

capacidad respiratoria máxima y no en relación con la saturación arterial de oxígeno.

5. En cinco enfermos estudiados antes y después de la comisurotomía mitral, tres mostraron una reducció de la presión arterial pulmonar y un aumento correspondiente en la capacidad máxima respiratoria.

6. Se discute la significación de las anormalidades de distribución y de difusión presentando tres casos demostrativos.

ZUSAMMENFASSUNG

1. Cardiale und respiratorische Untersuchungen von 61 Kranken mit reiner Mitralstenose werden vorgelegt.

2. Die 61 Kranken werden in 4 Gruppen eingeteilt entsprechend der Höhe des mittleren pulmonalen Arteriendruckes. Die respiratorischen Messungen variierten erheblich in Beziehung zum pulmonalen Druck. Die Vitalkapazität wies die engsten Beziehungen auf zum pulmonalen Arteriendruck und Wiederstand.

3. Kranke mit niedrigen pulmonalen Arteriendruck fallen in 2 Kategorien; nämlich diejenigen mit minimaler Mitralstenose und diejenigen mit klinisch latenter Linksinsuffizienz. In beiden Unterteilungen dieser Gruppe blieben die Lungenfunktionsprüfungen meist innerhalb der gemäss Grösse und Alter vorbestimmten normalen Grenzen.

4. Das Ausmass der Kurzatmigkeit ergab eine engere Beziehung zur Höhe des pulmonalen Arteriendruckes und zur Vitalkapazität als zum Atemgrenzwert und stand in keinem Bezug zur arteriellen Sauerstoffsättigung.

5. Von 5 vor und nach mitraler Commissurotomie untersuchten Kranken zeigten 3 eine Herabsetzung des pulmonalen Arteriendruckes und eine entsprechende Zunahme des Atemgrenzwertes.

6. Die Bedeutung von Abnormalitäten der Verteilung und Diffusion wurden besprochen und an 3 Fällen veranschaulicht.

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The Rehabilitation Team in a Tuberculosis Hospital: Psychosomatic Aspects*

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Most tuberculous patients at the National Jewish Hospital are ambulated early during the course of intensive combined drug therapy. This practice is based upon the evidence that the available antimicrobial agents are sterilizing only for multiplying tubercle bacilli, and upon the evidence that most isoniazid-resistant mutants of tubercle bacilli have strictly limited pathogenicity for most tuberculous patients. Thus it is believed that bed rest, except for toxic and febrile patients, is actually contraindicated.[1-6] Therefore, rehabilitation is initiated soon after admission and initiation of drug treatment. Formerly, a patient, after a year or two or more of hospitalization could look forward to discharge on four hours of "work tolerance"—which in practical terms seldom meant economic or social self-sufficiency but an indefinite, additional period of convalescence and dependency.

Today, under our Pilot Program† patients are being discharged fully rehabilitated to the point of an eight hour work day.

The first step in our rehabilitation program is always that of emotional rehabilitation, in the sense that good case work leads to the development of proper motivation and attitudes. The next step is that of physical hardening, beyond which some patients (those who have adequate settings to which to return) need not go. The third step (for most patients) is that of vocational rehabilitation, which may involve vocational re-training in a completely new occupation more suitable to the individual's physical capacities and emotional needs or brushing up and regaining of old skills.

Tuberculosis, it has been said, serves the unconscious needs of some patients so well that infection with the bacillus is less a stroke of fate than a kind of pact with the devil. "If tuberculosis germs are virtually everywhere," Dunbar[7] asks, "why is it one person never gives the germ a chance and another seems to provide a virtual broth culture in which they thrive?" In the absence of a convincing answer on the immunological level, the psychiatrist ventures that "even in the matter of bacterial infection it takes two to make a bargain."[8] In short, "tuberculosis is often

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†Pilot Program—Average length of stay at hospital is now 8 months at which time patients have attained four-hour-work tolerance. In 18 months to two years then, it is possible to take patients with active pulmonary tuberculosis, inactivate that process and rehabilitate to the point where they can step from the hospital into a full, eight hour employment situation. Utilizing this opportunity, the hospital has for the past two years maintained a Pilot Program, under which some 25 patients at any given time, who are in need of vocational rehabilitation, are being kept at the hospital until completion of the vocational program. This enables them to step directly from the hospital into full employment.

clearly a form of unconscious suicide on the part of the patient who has conflicting wishes both to live and to die" and "gratifies the latter—underhandedly as it were—in a capitulation to the bacilli of Koch."[9] These cases, though not rare, are perhaps extreme. Generally, however, one can say of patients with tuberculosis that they also have *problems with dependency*. Sometimes there is conflict of dependency drives versus drives for independence; sometimes more or less frank surrender to dependency strivings, sometimes reactive hostility consequent upon the thwarting of these needs. As pointed out by Benjamin, et al,[10] dependency conflicts are well nigh universal in our culture; and regardless of the premorbid situation and personality structure of the patient, the treatment itself (up until recently) and the sequelae of tuberculosis, in terms of reduced work and earning capacity, all exaggerated dependency problems. Thus, much of the conflict, though perhaps unavoidable by the very nature of the disease, was nevertheless iatrogenic, socio-economic, and essentially *ex post facto* to the disease.

Today, for the first time, the dependency-encouraging factors have been enormously reduced—provided hospital staff and patients are willing to give them up. As we shall see from the following case illustrations, the average patient now at National Jewish Hospital is faced with the new necessity not for sloughing off responsibility but for assuming it and planning for relatively early self-sufficiency.

Case 1: illustrates case work therapy with the goal of helping the patient to overcome emotional obstacles which had long prevented her from using her artistic interests and talents for a gratifying vocational program.

She is a 31 year old single woman whose first breakdown with tuberculosis occurred when she was 16 years old. She had never been able to make a satisfactory life adjustment because her family situation had failed to meet her legitimate dependency needs. Instead, this personality was forced to use illness as a means of gratifying those needs. During her first hospitalization at National Jewish Hospital from 1948 to 1949, she refused social work help, other than referral to Colorado Division of Vocational Rehabilitation. This facility enabled her to take a nine months' business course at home following discharge from the hospital, but she was unable to succeed in such employment because she had to give up job after job due to illness. She became depressed over repeated failures and this was her frame of mind when reactivation of tuberculosis was diagnosed and she was readmitted to National Jewish Hospital in 1952.

While she was more amenable to casework this time, for the most part she focused discussions around striving for independence through a satisfactory vocational program. The recurrent theme which ran through her interviews with the social worker was feelings of disappointment at the hands of adults who had forced her to assume responsibilities for which she had not been ready. At the same time, she repeatedly expressed preference for a vocational program which she considered acceptable to the authoritative persons in her life, to the exclusion of a program which would obviously enable utilization of her artistic interests and talents. She would rationalize preference for the former on the grounds that those were more practical vocational plans for her since the art course, which she really wanted, was unattainable because her family would not support it.

Beneath all this lay the wish to remain indefinitely in the protected environment of the hospital. For help in solving this dilemma her problem was presented at a psychosomatic conference* for consideration by the consulting psychiatrist and the entire

*Psychosomatic Conference—These conferences, scheduled at regular intervals, are conducted by the consultant psychiatrist and attended by the entire staff. They are used to discuss special difficulties presented by patients which need interpretation to the staff with the object of effecting modifications of staff attitudes. The social worker presents pertinent data about the patient and information is pooled from all those present who know the patient. The psychiatrist uses this information to elucidate the dynamic significance of the patient's behavior. The group process in the discussion allows for ventilation of counter-transference problems on the part of the staff.

rehabilitation team. In the discussion some members seriously questioned whether this patient had the ego strength to tolerate the insight necessary to enable her to recognize her dependency strivings. (Incidentally, it was interesting to observe the rejecting attitudes this discussion provoked in some staff members whose own dependency needs were apparently reactivated.) They held strongly to the view that she was not good material for the Pilot Program. The psychiatric members of the team insisted that she should at least be offered the opportunity provided by this program to test her capacity.

For the next two months she was unable to progress in vocational planning, but the social worker was able to help her ventilate her demands that her family gratify her dependency needs. She was then able to recognize that this involved change on the part of her family which she could not realistically expect of them. This impasse was finally solved by her recognizing that *she* was the one who would have to change. She then considered a commercial art course, which would involve limited support from her family, with which they were willing to go along. After embarking on this program, she was free enough to express her real wish for a longer program of training as an art teacher. The supportive permissiveness with which this wish was accepted by the hospital and the Division of Vocational Rehabilitation enabled her to take advantage of an opening on the staff for a part-time evening telephone operator. With this part-time job, she was able to relinquish her need for further financial dependence on her family.

Now she is earning her maintenance and a small monthly stipend by part-time work on the switchboard, while pursuing a course in art education at Denver University. We have achieved with her the objectives of the Pilot Program, in that she is actively engaged in a personally gratifying rehabilitation program while under cover of antimicrobial drugs and under medical observation.

Formerly, we saw numbers of patients who "used" tuberculosis to gratify urgent dependency needs and internalized hostility, cling willy-nilly to their illness, yielding it up neither to bed rest nor to surgery. Now, it is possible that streptomycin, isoniazid, the newer resective techniques and newly oriented staff *will* forcibly deprive them of the disease and its regressive satisfactions. Will they turn elsewhere for their needs—to acting out, to other psychosomatic ills, to neurotic syndromes? It is not only theoretically possible, but we have seen it more than once. Such patients seem to have a ready bag of psychosomatic and psychological tricks at their beck and call. Their tuberculosis controlled, they turn easily to ulcers, colitis, migraine, depression, or what not, to gratify their dependency needs. They really have defense in depth. If such persons are ever to be genuinely rehabilitated and are not to become psychological casualties of the new tuberculosis cures, the hope lies in an enlightened rehabilitation program with emphasis on casework and occasionally even long term psychotherapy.

Case 2: illustrates the patient whose early strivings for recognition were frustrated within the family and reasserted themselves during hospitalization. Again unrecognized and unmet during the first two years of hospitalization, the related hostility was turned against himself by this passive, introverted personality. He was a 45 year old white, divorced man who was admitted to National Jewish Hospital in September, 1950. Two years later, at the time when he was coming up on activity preparatory to discharge, the medical director specially referred him to social service because of his obvious depression and psychological unreadiness to leave the protected environment of the hospital.

Up to that time he had been seen only once by a social worker for a brief service. Since the medical staff had found him to be a cooperative, conforming, undemanding patient, his urgent emotional needs were overlooked by an understaffed social service department. However, he was intensely absorbed in leather work in the occupational therapy shop. An occupational therapy note in December, 1951, said "It is evident that patient is hungry for encouragement and friendship. He appears anxious, depressed and withdrawn."

Beginning in September, 1952, the social worker saw him for four successive weekly interviews and thereafter at every opportunity. At first he was unable to talk and the social worker had to take the initiative to explain the medical director's concern about his apparent unhappiness; that although he would soon be on a four hour work tolerance, the hospital could not discharge him without knowing what was troubling him and what was facing him after discharge. In this and in the next interview, it was apparent that he was suffering from overwhelming feelings of inadequacy, rationalizing these in terms of inability to assume proper paternal responsibilities because of tuberculosis. Before the close of the second interview, the worker cut through his rationalizations, verbalizing his feelings of having been neglected by his family. She questioned the contradiction between these feelings and the evidence given by his family of warm interest in him from their letters to the hospital. This released his long-suppressed resentment against his family for having ignored and belittled his artistic interests and having forced him to concentrate on learning a trade by which

he could become self-supporting. He had compromised by becoming a sign-painter. The worker's sympathetic interest enabled him to express his rebellious opposition to resuming sign-painting following discharge. This explained why he had so constantly occupied himself with leather tooling at the hospital, he insisted that this was the only vocation he would accept after discharge.

The worker, perceiving his conflict between need to be an adequate father and need to express his artistic yearnings through leather work, enabled him to relax his drive immediately to prove his adequacy as a father. From this, he moved to a consideration of realistic rehabilitation plans as likely to be the quickest route to assumption of paternal responsibilities. He was able to concentrate on how he could utilize his leather work as a means of earning a livelihood.

His vocational interest was then discussed at a discharge planning conference.* In addition to counselling from the division of vocational rehabilitation representative, every available hospital facility was mobilized to help him feel that the whole staff was sympathetic to his strivings and interested in helping him achieve goals within realistic limits. He responded to this with obvious lifting of his depression and freer verbalization. He was seen more in the company of other patients from his home state, some of whom he instructed in their leather work.

The staff's active assistance in providing him with leads to local leather goods and saddlery firms enabled him to explore this field to his own satisfaction. He was finally able to compromise on plans for developing a small market for tooled leather saddle equipment and harness repairs among the large ranches in the vicinity of his home, and corresponded with his father and brothers to explore post-discharge plans with them.

Two months after the social worker's initial talk, he cheerfully volunteered that he had come to the conclusion that he would be able to develop a satisfactory plan for himself in Texas wherein he could continue his leather work but fill in with sign-painting in order to make money, provided he could also set up a little business on the side for his leather work. His father offered to make available a two-room house for his leather work. Late in November, he surprised his social worker with the announcement that he had decided to spend the holidays at home with his family and asked that transportation arrangements be made for him as soon as possible. He was discharged on December 4, 1952 in good physical condition, on four hour work tolerance, and in good spirits, though with obviously mixed feelings of elation and apprehension.

One may speculate what a serious psychological casualty this patient might have become had he not had the release afforded him by occupational therapy prior to the social worker's intervention and the mobilization of the total hospital facilities in the belated effort to buttress such ego strengths as he still retained. The new therapeutic milieu calls for staff who can accept the dependent patient and the rebellious one, the helpless and the hateful—not with indulgence or counterhostility but with active curiosity and good will. How did he get this way? Is there some way I can help him work it out or get beyond it?

Case 3: illustrates the young patient not yet too damaged psychologically, of whom it may perhaps be said that she had the good fortune to enter a tuberculosis hospital at a time when definitive medical and surgical treatment were available and when the emphasis was upon total rehabilitation rather than on debilitation. This patient, age 19 years, is an attractive, petite, dark-complexioned Spanish-American girl. She is a warm, lively, friendly individual, who soon became popular among the patients. She is the youngest of three children, and as long as she can remember, her family has been living in a rough congested section of New York City. Since her father's death

*Rehabilitation and Discharge Planning Conference—This hospital's practice is to begin rehabilitation and discharge planning as soon as feasible after admission. These conferences, held bi-monthly, are conducted by the medical director and attended by the medical staff, social workers, occupational therapists and the state representative of the division of vocational rehabilitation. The social workers present for discussion those patients who they consider are ready for rehabilitation planning, and the physicians review the patients' medical status. If the patient is considered to be medically ready to begin rehabilitation planning, the social worker presents the patient's educational and vocational background, along with the patient's own ideas regarding a suitable vocational program. The occupational therapists present their observations of the patient's interests, aptitudes and skills and the division of vocational rehabilitation representative contributes his knowledge of the availability of suitable training facilities, and the practical employment possibilities. When agreement is reached by the group, on the basis of these objective criteria, that the patient is ready for at least exploration of a vocational program, the patient is scheduled for an appointment with the division of vocational rehabilitation representative. As planning with the patient progresses, cases are brought back to the conference for revaluation as the need arises.

when she was 10 years old, her mother has had to work outside the home. She was discovered to have tuberculosis shortly after her father's death. From that time until her admission to National Jewish Hospital in July, 1952, with the exception of two years, nine months of hospitalization her tuberculosis was treated in out-patient clinics while she rested at home. Despite these vissicitudes in health, she managed to complete seven terms of high school, where she maintained a B average. She could not have many friends because of physical inability to run around with them and, besides, she maintained that she liked school and preferred to take studies seriously although she did not know what she wanted for herself vocationally. By the time she arrived at National Jewish Hospital, she had already spent nine years fighting tuberculosis and expressed discouragement about her repeated school interruptions and the many years already lost of her young life. She was now 19 and full of doubts as to whether she would ever be able to complete high school, get a decent job, meet other young people with similar interests and lead a normal life. She felt she had already lost too much time without being able to reach any of her goals to surmount the socio-economic deprivations she so keenly felt.

She was elated when she found that she could continue her high school studies at National Jewish Hospital. She took her studies seriously and procured her high school diploma in the summer of 1953 from the Denver Department of Education, which maintains an accredited teacher at the hospital. She participated actively in the patients' council. In fact, she was one of its candidates for president in the summer of 1953 and was defeated by a single vote. She remained active on the entertainment committee, has successfully taken part in several of the patients' shows and has led an active social life with her contemporaries of both sexes. In the meantime, she made fruitful use of an intensive, supportive relationship with her social worker at the hospital, who helped her weather successfully a number of crises in her family, while her mother was helped with these problems by the social worker in the New York office of National Jewish Hospital. The hospital social worker and her participation in the pre-surgical group* helped her get through surgery with flying colors. With the aid of vocational counselling from division of vocational rehabilitation, she is now contentedly pursuing a course of training as a medical secretary in one of Denver's business schools. She is due for discharge from the hospital in June, 1954 with eight hours' work tolerance, in possession of a high school diploma and fully equipped to take a job as a trained medical secretary. This patient does indeed seem to have made up for "the lost years."

What of the future? Psychiatrist and caseworker do not constitute a rehabilitation team. Only through staff personnel generally can one provide a therapeutic milieu. Space permits just a hint or two of what this involves. There is often an over-determinism to the choice of tuberculosis treatment as a profession, just as there is to the "choice" of tuberculosis as an illness. Many sanatorium staff members have themselves been patients, and one assumes that such factors as the need for a relatively sedentary way of life and reluctance to leave the familiar security of the sanatorium walls play a role here. On further observation and reflection, it becomes apparent that there is often a rich psychological interplay between the needs of the patient and the needs of the physician or nurse who was once such a patient. Regardless of new drugs and new surgical techniques, the doctor will tend to infantilize patients, or needlessly restrict them, or unconsciously engage them to act out rebelliously, if he is reacting blindly in terms of his own old needs as a patient. On the other hand, a therapeutic milieu can use to very good advantage former-patient staff doctors, nurses,

*Pre-surgical Group—This group, held weekly, at which attendance is voluntary, is designed essentially with psychotherapeutic objectives for those patients considered to be candidates for major surgery. The group is conducted by the staff psychologist, with the assistance of the chief resident surgeon who answers specific medical questions raised by patients. Although the ostensible purpose of the group is patient education, the group leader encourages ventilation by the patients of their feelings and attitudes toward surgery. As far as possible, reassurance is given through the group discussion. Post-operative patients have also been invited to attend as they have been found to contribute effectively to the psychotherapeutic results.

and others (who are themselves truly rehabilitated) with whom the patient can identify. Helping our staff to minimize their projections, handle their own dependency needs and reactive hostility, and see the patient in a realistically helpful light is, and will continue to be, the constant goal of our in-service training.

Discussion

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In the case histories of this interesting paper we can observe how a well-equipped institution with a highly trained staff and an adjustable program can be mobilized to participate in the rehabilitation of patients with a psychosomatic illness. With the innovations in the medical and surgical treatment of tuberculosis, these workers have devised a program suitable for the needs of patients who will return to the community in a relatively short period of time and avoid the debilitating effects of institutional withdrawal.

We also observe that the psychotherapeutic portion of the program is based upon the recognition that the character types of patients developing tuberculosis are not of a single pattern as they are described as the helpless, the rebellious and the hateful. It is difficult to imagine how *any* type of individual would not be lured to some degree of acceptance of the regressive satisfaction of withdrawal from the responsibilities of life if such an opportunity were suddenly offered. With the advent of more active therapy requiring a shorter period, this temptation must be confronted as a major obstacle in the rehabilitation program.

It appears in the program described, the social caseworker has assumed a central coordinating position. In my opinion, this is a most appropriate choice as the professional person who has been trained specifically to grasp the subtleties of the environmental demand of the community in addition to the psychodynamic conflicts of the individual. This arrangement avoids the difficulty of forcing an unwilling patient to accept direct psychiatric treatment which, in many cases, would represent an exaggeration of one aspect of their total problem.

This paper raises the interesting question of the effect of the introduction of a rapid therapy program in a chronic hospital which has been attuned to a slower pace. There is one side effect inferred, although not specifically mentioned, which we have observed in clinical psychiatry in recent years. I am referring to the optimistic attitude which develops among the members of the staff of the hospital when positive therapeutic measures are introduced. Certainly our state hospitals for the mentally ill exhibit a far different atmosphere than was prevalent even 15 years ago. I think that most psychiatrists would grant that such optimism is an essential ingredient of psychological treatment whether the illness is tuberculosis or schizophrenia. At the other extreme, it is possible that such a trend may lead to a new type of problem, if an excessive amount of pressure is brought to bear on passive-aggressive patients, mobilizing their obstructing defenses.

Of direct interest to the clinical psychiatrist is the important problem of rehabilitation in mental illnesses. If one views such illness as a form of decompensation, of varying degrees, in the face of a personal-biological crisis, it must then be asked how much regression should be encouraged, how long should this be permitted and how can a patient be restored to a feeling of individual identity, relieved of constricting and distorting emotional bonds. These questions have become the rational foundation of a humane scientific hospital program. I believe the paper we have heard has provided many stimulating leads in these problems.

It is to be hoped that as their experience lengthens, these workers will make further contributions to our understanding of the therapeutic processes of support and restoration.

SUMMARY

Newer medical and surgical measures in the field of tuberculosis are changing the psychological problems of treatment and rehabilitation. At the National Jewish Hospital at Denver, patients are put on increasing ambulatory activity, regardless of the extent of the illness, within three to eight weeks after admission. Whereas formerly doctors had to encourage patients to accept long periods of inactivity and a passive orientation, now there may be the problem of the patient who clings to his illness because it meets his needs for dependency. If the treatment cures his tuberculosis in spite of his unconscious needs, he tends to develop other psychosomatic complaints. A rehabilitation team, including psychiatrist and social workers, helps not only patients but personnel to overcome the psychological barriers to real rehabilitation.

RESUMEN

Los nuevos recursos médicos y quirúrgicos en tuberculosis están cambiando los problemas psicológicos del tratamiento y de la rehabilitación. En el Hospital Nacional Israelita de Denver, los enfermos se ponen en actividad ambulatoria creciente sin tener en cuenta la extensión de la enfermedad, después de tres a ocho semanas de admisión. En tanto que antes los doctores tenían que alentar a los enfermos para que aceptaran largos períodos de reposo, ahora puede haber el problema del enfermo que se apega a su enfermedad porque le sirve para mantenerse. Si la tuberculosis es curada a pesar de sus necesidades inconscientes, tiende a presentar otras manifestaciones psicosomáticas. Un grupo de rehabilitación, incluyen do psiquiatras y trabajadores sociales, ayuda no sólo a los enfermos sino al personal para dominar las barreras psicológicas que se oponen a la rehabilitación verdadera.

RESUME

Les nouveaux procédés médicaux et chirurgicaux dans le domaine de la tuberculose sont en train de changer les problèmes psychologiques de traitement et de réadaptation. A l'Hôpital National Israélite de Denver, les malades reprennent progressivement leur activité ambulatoire, quelle que soit l'importance de leur atteinte, dans un délai allant de 3 à 8 semaines

après leur admission. Tandis qu'autrefois les médecins devaient encourager les malades à accepter de longues périodes d'inactivité et une attitude passive, maintenant le problème suivant peut se poser: celui du malade qui s'accroche à sa maladie parce qu'elle satisfait son besoin de dépendance. Si le traitement guérit sa tuberculose, malgré ses besoins inconscients, il a tendance à développer d'autres troubles psychosomatqiues. Une équipe de réadaptation, comprenant un psychiâtre et des assistantes sociales aide non seulement les malades mais aussi le personnel médical à surmonter les barrières psychologiques qui s'opposent à une véritable réadaptation.

ZUSAMMENFASSUNG

Neuere interne und chirurgische Massnahmen auf dem Gebiet der Tuberkulose sind im Begriff, die psychologischen Probleme der Behandlung und Wiedereingliederung in den Arbeitsprozess umzugestalten. Am Nationalen Israelitischen Krankenhaus in Denver werden die Kranken unbeschadet der Ausdehnung des Prozesses innerhalb von 3-8 Wochen nach der Aufnahme auf zunehmend ambulantes Verhalten umgestellt. Während früher die Ärzte den Kranken Mut zuzusprechen hatten, lange Zeiträume der Inaktivität zu akzeptieren und sich passiv zu verhalten, kann sich nun das Problem des Kranken erheben, der sich an seine Krankheit klammert, weil sie mit seinem Bedürfnis nach Abhängigkeit zusammentrifft. Heilt die Behandlung seine Tuberkulose trotz seinem unbewussten Verlangen, so neigt er dazu, andere psychosomatische Beschwerden hervorzubringen. Eine Rehabilitations-Gemeinschaft einschliesslich Psychiater und sozialen Fürsorgern hilft nicht nur den Kranken, sondern auch dem Personal, die psychologischen Hindernisse zu überwinden, die einer wirklichen Wiedereingliederung in den Arbeitsprozess entgegenstehen.

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Geographic Variation in the Prevalence of Histoplasmin Sensitivity

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Since the demonstration in 1945 of an association between pulmonary calcification and histoplasmin sensitivity by Palmer[1] and Christie and Peterson,[2] numerous clinical, laboratory, and epidemiological investigations have increased the existing knowledge of histoplasmosis. It is now accepted that histoplasmosis, hitherto known only as a rare and fatal disease, also occurs in a benign and relatively common form; that the infective episode itself usually passes unrecognized; and that a positive skin reaction to histoplasmin, and, less frequently, pulmonary calcification are usually the only testimony of a previous infectious experience. While histoplasmin cross-reacts with coccidioidin and blastomycin, the relative rarity of coccidioidomycosis and blastomycosis leaves the bulk of the positive reactions to histoplasmin specific for infections with H. capsulatum. With these facts established the skin test has become an important epidemiological tool in the study of histoplasmosis.

Geography has played a prominent role in epidemiological investigations of histoplasmosis since comparisons of different locations by Palmer[3] first showed wide variations in the prevalence of positive reactors. That where one lives influences the probability of being infected with H. capsulatum more than how one lives or with whom is the logical conclusion stemming from statistical evidence based on skin-testing studies carried out in the years since 1945. The slightly higher rates among males,[4] among siblings of a positive reactor,[5] among rural populations,[6] and among whites,[4] are all relatively small compared with the variations among groups tested from different geographic areas.

There are now available in the literature reports of a number of studies that illustrate the general characteristics of the geographic variation in histoplasmin sensitivity in the United States. It is generally known that people who have spent most of their lives in the mid-central States are much more frequently sensitive to histoplasmin than persons living in other parts of the country; that the highest frequency of reactors occurs in the central Mississippi River Valley; that prevalence tends to decrease with distance from the area of highest frequency; but that wide variations sometimes occur within relatively short distances. Wide differences in the prevalence of histoplasmin sensitivity within the state of Tennessee have been reported by Christie and Peterson.[7] Furcolow and Sitterley[8] showed that in Kansas prevalence drops sharply as one moves westward from the endemic area in the eastern part of the State. Prior and Allen[6] showed similar variations in Ohio, with the highest prevalence in the southwestern

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part of the State. Beadenkopf et al[9] found a large proportion of lifetime residents of southern Illinois reacted to histoplasmin, with much lower frequencies in the northern half of the State. In Pennsylvania, Aronson[10] has found a relatively high rate of histoplasmin reactors in the southwestern part of the State and a gradual decrease in the prevalence of reactors over the rest of the State.

Material from a single locality or even a single state may provide valuable clues on the nature and extent of association between the prevalence of histoplasmin sensitivity and geographic factors. However, the range of geographic factors is obviously limited by the size of the area: material covering the span of an entire continent provides a greater opportunity for perceiving associations that could be obscured in a smaller area. But it is not entirely simple or safe to combine the results of independent studies of different areas into a larger geographic picture. Although each study of a particular locality may provide a reliable picture of the area covered, specific comparisons with other areas raise questions of differences in methods of testing and reading reactions, in criteria of classifying residence, in the product used, and in methods of analyzing the data that might account for the geographic differences found. To provide uniformly collected material on the entire United States, the Public Health Service augmented material obtained through its study of antigen sensitivity among student nurses by undertaking surveys with identical techniques among other groups of young adults.

The Field Studies Branch of the Tuberculosis Division* enlisted the cooperation of the United States Navy and numerous colleges and universities in studying large numbers of young adults through programs already established for routine examinations. Chest x-ray films, skin tests with tuberculin, coccidioidin, and histoplasmin, and a detailed residence history for each individual, provided that material for studying various aspects of the problem of antigen sensitivity and its relation to pulmonary pathology.

The present paper deals only with the results of the histoplasmin tests and the relation of positive reactions to location of lifetime residence for young adults from all over the United States.

A nation-wide mapping of histoplasmin sensitivity may serve several purposes: it provides a common point of reference for independent investigations carried out in different localities; it may expose geomorphological features which directly predispose to high prevalence of the infection; it could reveal geographic conditions acting directly on a vector as yet unrecognized; and finally, it gives a fairly reliable picture of the distribution of infection at the midpoint of the 20th century, a base line for future measurements which should detect either changes in prevalence within unchanging geographic boundaries or shifts in boundaries themselves through spread of the infection to new localities.

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Material and Methods

Material for the present paper is derived from results of histoplasmin skin tests and residence history data obtained from three sources: (1) 21,867 student nurses, of whom 20,698 were tested with histoplasmin between 1945 and 1949 in connection with a long-range study of tuberculosis among student nurses in 76 training schools located in 10 metropolitan areas in different parts of the country, (2) 49,102 students of both sexes, mainly college freshmen, in 34 schools tested between the years 1947 and 1950, and (3) 88,928 male Navy recruits tested between 1949 and 1951 as they entered the San Diego Naval Training Station from widely dispersed areas of the country. Altogether, histoplasmin skin test results are available for a total of 159,897 young adults tested between 1945 and 1951.

Histoplasmin Tests. Although the testing was done in many different places and at different times, efforts were made to assure uniform procedures. Throughout the studies certain basic standards were prescribed and, with minor exceptions, maintained. All tests were made by the intradermal injection of 0.1 cc. of histoplasmin in the volar surface of the forearm. Almost all reactions were read at 48 hours by measuring the transverse diameter of erythema and induration in millimeters; the measurements were recorded on the individual record forms provided by the Public Health Service. For purposes of the present paper, reactions of 5 or more millimeters of induration were defined as positive. All but 2 per cent of the tests were given with histoplasmin identified as H_{15}, H_{40}, and H_{42}.* When the supply of H_{15} became inadequate, H_{40} and H_{42} were prepared. Both lots were standardized against H_{15} and dosages adjusted to be equivalent to H_{15}.[11]

In the critical matter of testing and reading, data from the nurses' study is undoubtedly the most uniform since most of the tests were given and the reactions read by two trained staff members of the Public Health Service who traveled from school to school. In the Navy program the major part of the testing and reading was done by a few hospital corpsmen carefully instructed and supervised by Public Health Service staff. In the college student program, where tests were given and read by personnel of the respective colleges and universities, uniformity in reading and testing methods was approached by the use of detailed written instructions and assistance at the beginning of each program by field representatives of the Public Health Service.

Residence Data. Residence histories were obtained at the time the skin tests were given. Each person was asked to list all places in which he had lived six months or longer, specifying for each the town, county and state, his age at that time, and the type of residence—farm or non-farm.

To pinpoint as closely as possible the place where sensitivity was probably acquired, the present study is based on that part of the test population

*All histoplasmin was prepared and supplied by the Public Health Service. In the early phase of the testing program the following lots were used: H_0 furnished by Dr. C. W. Emmons, National Institutes of Health, and H_0, H_1, H_2, H_4, H_5, H_6, and H_7, by Dr. Arden Howell.

that could be classified as lifetime residents of single counties. The county was selected because it is the smallest identifiable unit that subdivides the entire geographic area of the United States. To be considered a lifetime resident of a particular county an individual must have lived within the boundaries of that county his entire lifetime except for periods of less than six months. Of the 159,897 persons tested, 73,536, or nearly half, said they had never been outside the boundaries of a single county for longer than six months at a time, and therefore were classified as "lifetime" county residents.

Characteristics of Test Population. To compare the prevalence of histoplasmin sensitivity among counties, the composition of the tested groups residing in the various counties should differ only with respect to characteristics associated with their place of residence. The test population included male Navy recruits, male and female college students, and female student nurses, each group probably representing a fairly wide range of social and economic backgrounds. However, these factors are not known to be associated with histoplasmin sensitivity and it is assumed that they have not affected the geographic distribution presented here.

The geographic distribution of histoplasmin sensitivity will, however, be affected by the presence of other fungus infections that cause sensitivity to histoplasmin: coccidioidomycosis[12] and, to a lesser extent, other infections such as blastomycosis may cause cross-reactions. Coccidioidomycosis is highly prevalent in the southwestern part of the country, and almost all of the lifetime residents of that area who reacted to histoplasmin were also sensitive to the coccidioidin test given at the same time. Blastomycosis, which is much less prevalent than coccidioidomycosis and apparently much more scattered, has probably had little influence on the frequency of histoplasmin reactions. Thus, with the exception of the southwest, where many of the histoplasmin reactions probably represent cross-reactions with coccidioidomycotic infection, the results of testing with histoplasmin can be taken as a fairly reliable index of specific infection with histoplasmosis.

Because age, and, to a lesser degree, sex and race are also factors which do influence the prevalence of histoplasmin sensitivity, their effect on the results presented here must be considered. Males outnumbered females

TABLE I

TOTAL NUMBER OF PERSONS TESTED WITH HISTOPLASMIN, NUMBER EXCLUDED, AND NUMBER USED IN PRESENT ANALYSIS, BY SOURCE OF DATA

Test Population	Total Number Tested	Multiple County Residence (Excluded)	Single County Residence	
			Not White or not Age 17-21 (Excluded)	White Age 17-21 (Used)
Total	159,897	86,361	5,084	68,452
Male	120,469	66,465	3,484	50,520
Female	39,428	19,896	1,600	17,932
Navy recruits (male)	88,928	47,673	2,151	39,104
College students				
Male	31,541	18,792	1,333	11,416
Female	17,561	8,636	1,024	7,901
Student nurses (female)	21,867	11,260	576	10,031

TABLE II

NUMBER OF ONE-COUNTY LIFETIME RESIDENTS TESTED WITH HISTOPLASMIN AND AVERAGE NUMBER OF TESTS PER COUNTY BY STATE

State	Number of Tests	Number of Counties	Average Number of Tests Per County
Alabama	1,520	67	23
Arizona	386	14	28
Arkansas	1,367	75	18
California	6,504	58	112
Colorado	1,629	63	26
Connecticut	111	8	14
Delaware	27	3	9
District of Columbia	58	1	58
Florida	1,183	67	18
Georgia	1,383	159	9
Idaho	490	45	11
Illinois	2,977	102	29
Indiana	2,694	92	29
Iowa	2,656	99	27
Kansas	4,765	105	45
Kentucky	1,445	120	12
Louisiana	1,614	64	25
Maine	74	16	5
Maryland	850	24	35
Massachusetts	647	14	46
Michigan	910	83	11
Minnesota	2,379	87	27
Mississippi	1,073	82	13
Missouri	3,185	115	28
Montana	586	57	10
Nebraska	1,280	93	14
Nevada	78	17	5
New Hampshire	24	10	2
New Jersey	491	21	23
New Mexico	478	32	15
New York	1,430	62	23
North Carolina	2,261	100	23
North Dakota	128	53	2
Ohio	4,605	88	52
Oklahoma	2,712	77	35
Oregon	690	36	19
Pennsylvania	2,452	67	37
Rhode Island	99	5	20
South Carolina	1,041	46	23
South Dakota	581	68	9
Tennessee	1,444	95	15
Texas	3,797	254	15
Utah	739	29	25
Vermont	15	14	1
Virginia	156	100	2
Washington	1,481	39	38
West Virginia	183	55	3
Wisconsin	1,458	71	21
Wyoming	316	24	13
TOTAL	68,452	3,076	22

by a ratio of 3 to 1, and predominated in most counties. In the few localities where females had a slight majority, rates among both males and females were low, and the differences between them slight. Therefore, although histoplasmin sensitivity rates are usually slightly higher in males, the effect of sex differences on these results has been minimal.

In order to make the material more homogenous, only data on white persons between the ages of 17 and 21 years were used. This limitation reduced the total of one-county residents to 68,452, as shown in Table I.

Geographic Representation. Most of the nation's 3,076 counties were represented in the population of 68,452 one-county lifetime residents, the numbers tested ranging from none in 206 counties to more than 40 in 356, as shown in the following table:

	Number of Persons Tested				
	Total	None	1 - 19	20 - 39	40 or more
Number of counties	3,076	206	2,034	480	356

Table II gives a general view of how the county representation was distributed by state. While the average number of persons tested per county in the western states was almost equal to the county average in the middle west, the coverage is better in the latter area because the counties themselves are much smaller in the middle west. This smaller county size makes it possible to define boundaries of areas of varying prevalence in the midwest more precisely than in the west. The test population contains relatively few lifetime residents of some states in New England and in the northwest.

The Problem of Random Fluctuations. The small number of persons tested in many counties meant that the percentages of positive reactors were subject to large random variations. It was desirable to find ways to reduce those variations—the effects of sampling errors—without obscuring significant geographic differences in prevalence. After experimenting with various methods, two procedures were applied to meet this problem.

The first of these is analogous to the "moving average" often used in plotting age curves. For each county, "contiguous" counties were defined as those touching it at any point or adjacent to a relatively small common body of water. By this definition, the average county had six contiguous neighbors, and the tested population for a specific county plus that of its contiguous counties was used in computing the percentage of positive reactors for that county. A few exceptions to the use of this procedure appeared desirable: percentages were based on single county data in several instances in southern California, Arizona and around the city of St. Louis, because in each case a contiguous county had an unusually large number of persons tested and also a very different rate of positive reactors. The use of the geographic moving average tended to eliminate small differences but smoothed out only slightly, we believe, significant geographic variations. The effect of this method of smoothing is limited to the distance of not more than one county.

A second adjustment was made when, in the course of actually mapping

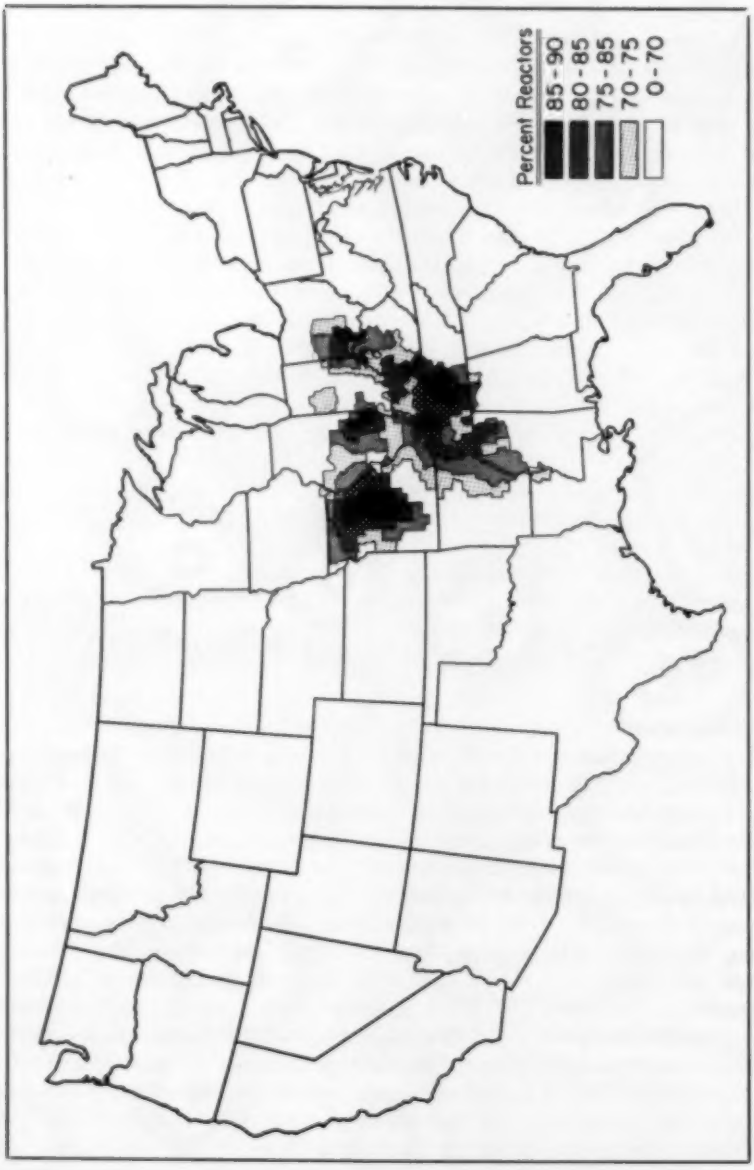
the prevalence of positive reactors, it was found desirable to group the rates of positive reactors. When counties were grouped within given percentage class intervals according to their computed rates, very small differences often would determine whether a county fell in one of two class intervals. Moreover, individual county rates were still subject to considerable sampling variability, even after smoothing by including contiguous counties. Therefore, an allowance of 2½ percentage points on either side of the computed rate for all counties whose rates were over 10 per cent was permitted in determining the class interval into which a county would be classified. For counties whose rates were under 10 per cent, a ½ point allowance was permitted. Within these conservative and arbitrarily selected limits, the judgment of the analyst determined whether counties whose rates fell sufficiently close to the boundary of a given class interval should go into that interval or the interval next to it. These adjustments were made only after the prevalence levels had first been plotted on maps with counties placed within the percentage intervals according to their computed rates. The permitted leeway was used only to remove small irregularities in the basic geographic pattern already established by the counties that fell with greater certainty within given percentage levels. For example, if a county with a rate of 51 per cent was surrounded by counties with rates between 40 and 50 per cent, it was placed in the 40—50 per cent class interval rather than the 50—60 per cent interval.

Large variations in the prevalence of histoplasmin sensitivity are known to occur within single counties[13] but such variations must necessarily be disregarded for the present purpose of mapping out a broad picture of the geographic pattern of sensitivity throughout the entire country.

Results

The frequency of positive reactors in the 3,076 counties ranged from 0 to a high of 90 per cent. The counties have been grouped into 12 percentage class intervals within this wide range. Since 12 classes do not lend themselves to easy visual discrimination in a single map, a series of maps has been required to show the entire range of geographic detail. In each of the first three maps, attention is focused on a certain part of the range and the class intervals above and below are compressed into two end groups. Each map shows the detailed geographic variation within one of three broad prevalence levels: Map 1—areas in which more than 70 per cent of those tested were positive reactors; Map 2—areas with from 40 to 70 per cent positive reactors; and Map 3—areas with less than 40 per cent positive reactors. These maps disclose the detailed features of geographic variation not discernible with the broader percentage classification used in the fourth map. This is a summary map, which presents a comprehensive picture of the distribution of histoplasmin sensitivity and shows the geographic boundaries of six major prevalence levels.

Map 1. In this map, where counties with rates lower than 70 per cent are not shaded, details are given for areas with rates above 70 per cent. The span between 70 and 90 per cent is divided into 4 intervals of 5



Map 1—Location of U. S. counties in which 70 to 90 per cent of young adult lifetime residents reacted to histoplasmin.

percentage points each, and the counties with rates in each of the 4 intervals are shown in shadings of increasing intensity.

Prevalence rates over 85 per cent are found in six locations. The largest area, in north central Missouri, includes 18 counties immediately west of the Missouri River and covers an area roughly 70 to 150 miles. Three smaller centers cluster along the Tennessee-Kentucky border. Six counties in eastern Illinois extending roughly 70 miles along the Wabash River, and 3 small counties in southern Ohio make up two other small areas.

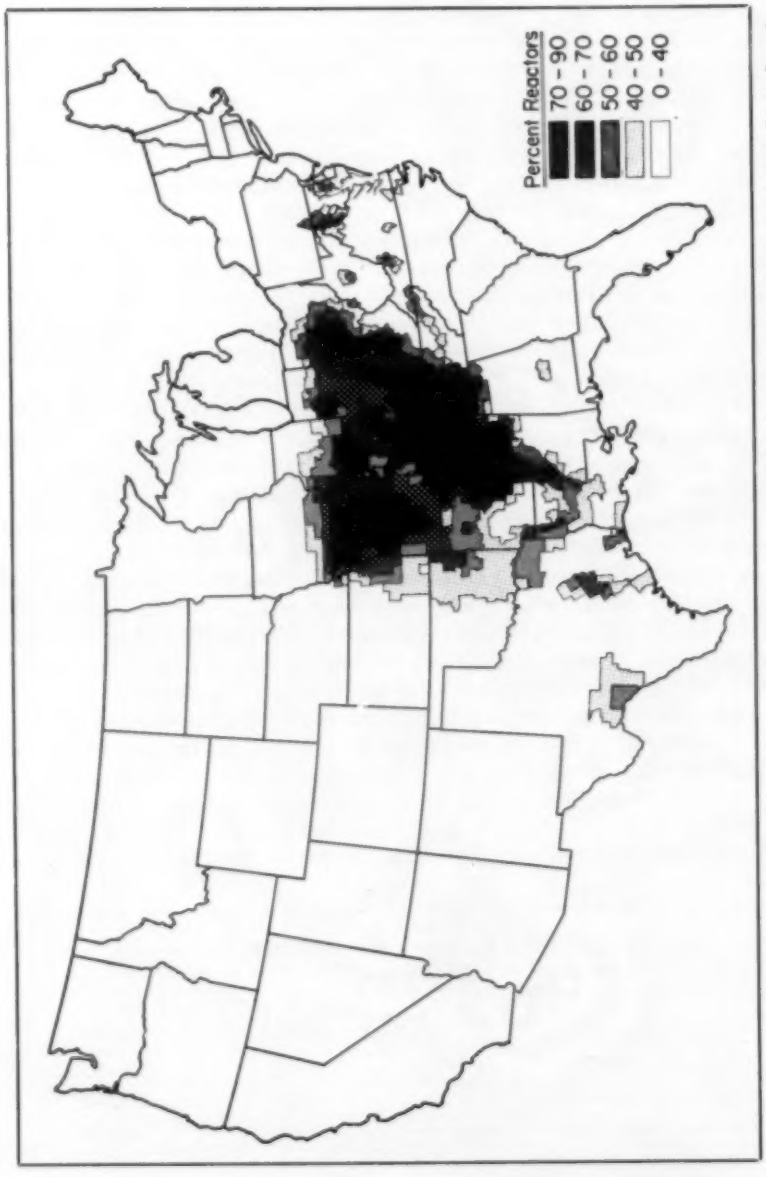
Certain similarities in geographic characteristics are apparent among these six centers which have in common histoplasmin reactor rates of over 85 per cent. Although they vary in size from 1,372 to 10,885 square miles, as shown in Table III, all centers are predominately agricultural with the exception of the city of Nashville in the central Tennessee area.

All six areas lie between the 35th and 40th parallels of north latitude, a difference of about 300 miles from the most southern to the most northern point. The climate is of the "continental" type, characterized by a rather large range of temperature from season to season and large variations in the amount of precipitation from year to year. The average annual rainfall ranges from 40 to 50 inches among the six areas. The average January temperature varies by only 10 degrees F. and the average July temperature by only 1.9 degrees F. The topography does not present sufficient differences in elevation to cause any marked peculiarity in climate. Elevation above sea level ranges between 500 and 1,000 feet.

Each of these six areas with histoplasmin reactor rates between 85 and 90 per cent is a center of generally very high prevalence which decreases gradually as one moves away from the center. The rapidity of the decrease in the surrounding areas appears to be related to the size of the center; for example, the over-85-per-cent area in Missouri, containing over 10,000 square miles, is surrounded by a ring two counties deep with rates between 80 and 85 per cent; while the small over-85-per-cent center containing less than 1,400 square miles, has only 3 neighboring counties with rates between 80 and 85 per cent. The small Tennessee-Kentucky border areas with rates over 85 per cent are linked by counties with rates between 80 and 85 per cent to form a narrow winding ridge. On the whole, counties

TABLE III
AREA AND POPULATION IN EACH OF THE SIX LOCATIONS WITH HISTOPLASMIN SENSITIVITY RATES OVER 85 PER CENT

Location	Area (Sq. mi.)	Population
Central Missouri	10,885	321,107
Central Tennessee	5,935	570,581
Eastern Illinois	2,529	121,655
Western Kentucky & Tennessee	2,419	116,688
Southcentral Kentucky	2,365	96,674
Southwest Ohio	1,372	76,314
TOTAL	25,505	1,303,019



Map 2—Location of U. S. counties in which 40 to 90 per cent of young adult lifetime residents reacted to histoplasmin.

with rates between 75 and 80 per cent are farther removed from the six centers, and, together with counties in the 70 to 75 per cent bracket, loosely connect the six centers and their surrounding 80 to 85 per cent areas.

Map 2. This map has been constructed to bring into sharp relief the geographic pattern of areas in which the histoplasmin sensitivity rates range from 40 to 70 per cent. Here, the 70 to 90 per cent areas, which are shown in detail in the first map, have been telescoped into a single group and are all shown in the darkest shade. The three progressively lighter shadings are used to show areas with rates in the intervals 60 to 70 per cent, 50 to 60 per cent, and 40 to 50 per cent respectively. All areas with rates below 40 per cent are unshaded.

The sum of all the shaded areas, representing all counties with rates above 40 per cent, forms an irregular shaped triangle in the eastcentral part of the United States. The northern boundary of the triangle follows the 41st parallel fairly closely across southwestern Iowa, Illinois, and Indiana into central Ohio. On the west, the edge of the triangle runs from southern Iowa slightly southwest through Kansas and Oklahoma to the northeastern corner of Texas. The third side of the triangle follows the Appalachian foothills southward through eastern Kentucky, central Tennessee, and the northern tip of Mississippi into northwest Louisiana.

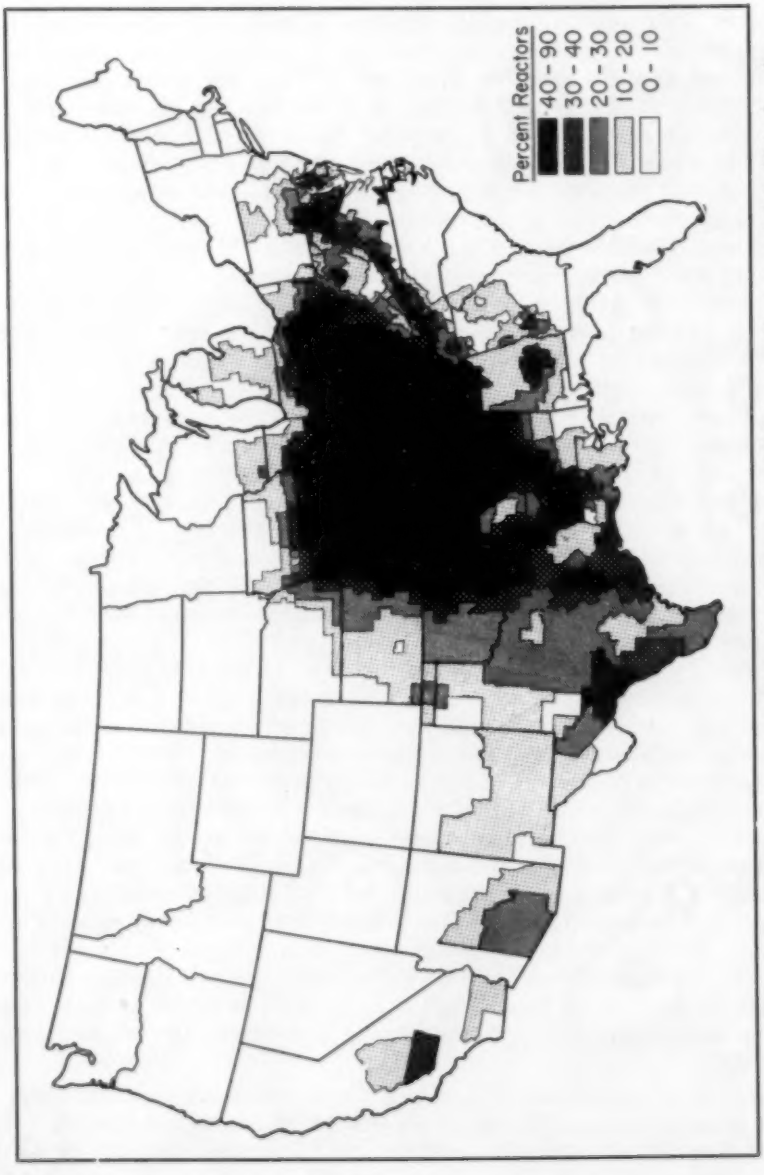
In general, the counties with rates between 40 and 70 per cent cluster closely around the region with rates from 70 to 90 per cent, with the 60 to 70 per cent areas forming an almost continuous ring around those with higher rates. A tendency is apparent for areas with high rates to follow the central Mississippi River system and its major tributaries, the Missouri, Ohio, and Tennessee.

A ridge formed by counties with rates over 40 per cent extends from the lower Mississippi Valley westward through central Louisiana and upward into Oklahoma, following the course of the Red River Valley to the Texas-Oklahoma border. Within the general region of high prevalence, a valley of lower prevalence begins in southern Illinois and extends south and west into southern Arkansas, where rates fall below 40 per cent.

This map shows also five small centers with relatively high rates that are somewhat isolated from the major endemic region. The most prominent is the strip which runs from the northern tip of Virginia across eastern West Virginia and Maryland into southern Pennsylvania. Another appears in southern Alabama where 3 counties have rates between 40 and 50 per cent. The remaining three occur in Texas, one along the Mexican border and two on the Gulf of Mexico, but there is some likelihood that at least some of the histoplasmin reactions actually represent cross-reactions with coccidioidin.

Map 3. In the third map, attention is focused on the geographic distribution of rates between 10 and 40 per cent, with a separate shading for each of three 10 point intervals. All counties with rates above 40 per cent are grouped in the single class shown in solid black, while all areas with rates below 10 per cent are unshaded.

The triangular shape of the area in which the prevalence of positive



Map 3 — Location of U. S. counties in which 10 to 90 per cent of lifetime residents reacted to histoplasmin.

histoplasmin reactors is over 40 per cent becomes more clearly evident in this map. Counties in the next lower class with rates between 30 and 40 per cent form a tight ring around most of the central endemic area. The high prevalence centers which were separated from the central core in the preceding map are now shown to be linked to it by counties in the 20 to 30, and 30 to 40 per cent class intervals. For example, the high prevalence area in northern Virginia, West Virginia, Maryland and southern Pennsylvania is connected with the central area by a narrow ridge arising out of Tennessee and stretching the length of the Virginia-West Virginia border. The center of high prevalence in southeast Texas which appeared on the preceding map is now revealed as part of a distinct ridge extending southward from the high prevalence area in eastern Oklahoma to the Gulf of Mexico along the course of the Brazos River.

The band on the western boundary of the central endemic area from Nebraska to Texas illustrates a basic characteristic of the geographic distribution, an orderly progression of decreasing percentages of positive reactors with increasing distance from the core.

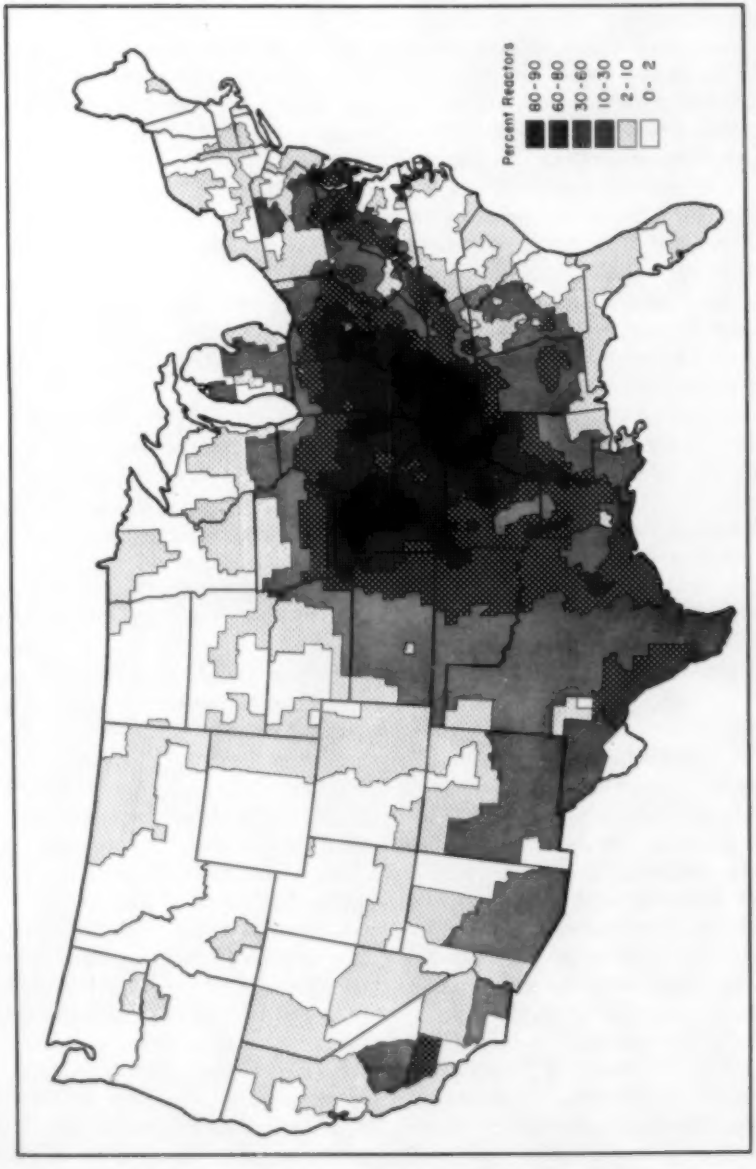
All or most of the histoplasmin sensitivity found in California, Arizona, and New Mexico probably represents cross-sensitization by infection with Coccidioides immitis.

Map 4. This map gives a broad summary view of the pattern of histoplasmin sensitivity across the nation. Areas with histoplasmin sensitivity rates ranging from 10 to 90 per cent are shown in four percentage class intervals, and the remaining areas, those with rates below 10 per cent, have been separated into counties having rates of less than 2 per cent and those with rates between 2 and 10 per cent.

Concentration and radiation, these are the two striking features of the summary map: the geographic localization of histoplasmin reactor rates over 60 per cent in a triangular area of the middle west and the radiation from the central core in all directions. It may be that the geographic pattern of diminishing frequency of reactors with increasing distance from the central area represents a dispersal of the etiologic agent from the focus along the paths of least geographic resistance. It could also be that the dispersal is not a completed, but a continuing process. The present mapping may represent a transitional picture of the spread of the fungus, Histoplasma capsulatum, just as other fungi, nonpathogenic for man but producing plant diseases, are known to have spread, some by natural and some by man-made means. Results of another survey at some future date in which the conditions of the present survey and analysis are duplicated should reveal whether the present boundaries have changed.

In Table IV, the 3,076 counties have been grouped according to the percentage of lifetime residents who were positive reactors to histoplasmin. The table also shows the total area in square miles and the total population of the counties in each prevalence interval, as well as the percentage that each group of counties possesses of the nation's total area and total population.

When the material in the table is considered in connection with the



Map 4—Distribution of U. S. counties according to per cent of young adult residents reacting to histoplasmin.

TABLE IV

AREA AND POPULATION OF GROUPS OF UNITED STATES COUNTIES, CLASSIFIED ACCORDING TO PER CENT OF REACTORS TO HISTOPLASMIN

Per Cent of Reactors		Number of Counties	Area (Sq. mi.)	Population	Per Cent of Total		Cumulative Per Cent of Total	
					Area	Population	Area	Population
85 - 90		51	25,505	1,303,019	0.9	0.9	0.9	0.9
80 - 85		103	46,372	2,892,089	1.5	1.9	2.4	2.8
75 - 80		125	60,119	4,205,959	2.0	2.8	4.4	5.6
70 - 75		116	56,568	3,724,238	1.9	2.5	6.3	8.1
60 - 70		133	67,724	4,793,469	2.3	3.2	8.6	11.3
50 - 60		118	72,797	5,373,513	2.4	3.6	11.0	14.9
40 - 50		150	104,755	4,133,202	3.5	2.7	14.5	17.6
30 - 40		174	118,773	7,849,818	4.0	5.2	18.5	22.8
20 - 30		292	234,118	9,367,984	7.9	6.2	26.4	29.0
10 - 20		448	397,716	19,805,898	13.4	13.1	39.8	42.1
2 - 10	West	313	539,526	8,170,706	18.1	5.4	65.3	69.3
	East	348	221,326	32,839,989	7.4	21.8		
0 - 2	West	392	812,986	15,754,927	27.3	10.5	99.9	100.0
	East	313	216,441	30,482,550	7.3	20.2		
TOTAL		3,076	2,974,726	150,697,361	99.9	100.0		

summary map, interesting features of the distribution of histoplasmin sensitivity emerge. The areas with rates of less than 10 per cent have been geographically subdivided in the table because these rates occur in two distinct locations, the heavily populated eastern seaboard, and the sparsely populated expanses of the west and northwest. An area in the east containing only 15 per cent of the total area of the United States but with 42 per cent of the total population shows the same prevalence rates, less than 10 per cent, as the region stretching from the Great Lakes to the Pacific and from the Canadian border to central New Mexico, with 45 per cent of the nation's area but only 16 per cent of its population. These differences in area and in population carry implications of other differences such as crowding, urbanization, occupations, industries and their atmospheric by-products, and whole patterns of living. The presence of equal proportions of histoplasmin reactors in spite of these area and population differences suggests that it is unlikely that histoplasmin sensitivity is closely associated with socio-economic factors.

In the areas in which less than 2 per cent of the lifetime residents reacted to histoplasmin, the causative agent may, for all practical purposes, be regarded as non-existent. Failure to find any significant number of positive reactors in such widely separated areas as Maine, central Florida and the Pacific Northwest suggests that the conditions necessary to support the existence of the causative agents are multiple, and that different conditions may fail to be satisfied in the widely differing geo-

graphic areas in which histoplasmin sensitivity is absent.

The separation of the areas with rates between 2 and 10 per cent from the areas below 2 per cent furnishes a pattern which should contribute to an eventual understanding of the etiologic puzzle. Statistically, the evidence indicates that the areas shown in gray do in fact have higher sensitivity rates than those shown in white, that these are not simply differences due to experimental error in the test or to errors in the residence histories. Much of the gray area borders on areas with rates between 10 and 30 per cent. There are also both islands in the midst of wide expanses in which practically no reactors are found, and arms stretching out from the areas of higher prevalence, such as the strip stretching from northern Kansas north to the Canadian border of central Montana.

SUMMARY

This paper reports the results of a detailed mapping of geographic variation in the prevalence of histoplasmin sensitivity throughout the United States. The material is based on histoplasmin skin tests of 68,452 young adults who were lifetime residents of single counties. The data on this group were drawn from observations on more than 150,000 persons x-rayed and skin tested with various antigens in three cooperative research programs directed by tuberculosis research workers in the Public Health Service.

Skin tests and residence histories were obtained, recorded and interpreted as uniformly as possible to provide comparable material on a large homogeneous population.

A summary map of the United States shows the area of highest prevalence, from 60 to 90 per cent positive reactors, in the central states stretching in a triangle from Ohio to Iowa, extending southeast through Missouri and Arkansas to Louisiana, with a third side cutting from Ohio southwest through Kentucky, Tennessee and Mississippi.

The rate of positive reactors decreases, on the whole, with increasing distance from this triangular area. An area of moderately high prevalence in which 30 to 60 per cent of the young adults tested were positive reactors, forms an uneven ring around the central triangle varying in width up to about 300 miles. Next comes a ring of intermediate prevalence ranging from 10 to 30 per cent and including a considerable area westward. Histoplasmin sensitivity was practically absent among lifetime residents of the Atlantic and Pacific coastal areas, except for scattered islands of fairly high frequency.

The present project was undertaken with the intention of supplying a nationwide map of histoplasmin sensitivity. Such a map is a requisite for studies of the determinative factors in the growth and spread of H. capsulatum, and in the conditions of its transmission to man. With some degree of precision, the localities of varying risk have been defined over the country's entire area of differing geographic and climatic conditions. This analysis explains neither why nor how human beings become infected with Histoplasma capsulatum but it does measure the variation in the risk of infection over the 3,000,000 square miles of the United States.

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Kansas City, Kansas: Bethany Hospital, Providence Hospital, St. Margaret's Hospital, University of Kansas Hospital.

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RESUMEN

Esta comunicación relata los resultados de una zonificación detallada de las variaciones geográficas que tiene la frecuencia de la sensibilidad a la histoplasmina en los Estados Unidos.

El material se basa en las reacciones cutáneas a la histoplasmina en 68,452 adultos jóvenes que han residido todo el tiempo en un solo condado. Los datos de este grupo fueron extraídos de la observación de más de 150.000 personas pasadas por rayos X y sujetas a reacciones cutáneas con varios antígenos por tres grupos cooperativos de investigación realizada por miembros del Servicio de Salubridad Pública.

Se obtuvieron las reacciones cutáneas y las historias de residencia registradas e interpretadas de manera uniforme, de modo que constituye el material de una población grande y homogénea comparable.

Un mapa resumido de los Estados Unidos muestra el área de mayor frecuencia, de 60 a 90 por ciento en los estados del centro que se extienden en el triángulo de Ohio a Iowa, hacia el sureste a través de Missouri y Arkansas hasta Louisiana con un tercer lado cortando desde Ohio hacia el suroeste a través de Kentucky, Tennessee y Mississippi.

La proporción de reactores positivos decrece gruesamente al aumentar la distancia afuera de este triángulo. Una área de moderada frecuencia en la que del 30 al 60 por ciento de los adultos jóvenes fueron positivos, forma un anillo irregular alrededor del triángulo central, teniendo este anillo un espesor de alrededor de 300 millas. Afuera de él se encuentra un anillo de frecuencia intermedia de 10 a 30 por ciento e incluyendo un área considerable hacia el oeste.

La sensibilidad a la histoplasmina fué prácticamente desconocida entre los residentes por toda su vida en las áreas costeras del Atlántico y del Pacífico excepto en áreas aisladas diseminadas que tienen relativamente alta frecuencia.

El presente estudio se emprendió con la intención de obtener un mapa nacional de la sensibilidad a la histoplasmina. Tal mapa es un requisito para los estudios de los factores determinantes del crecimiento y diseminación del H. capsulatum y de sus condiciones para la transmisión al hombre. Con cierto grado de precisión las localidades de riesgo variable se han definido sobre el área completa del País, áreas de diferentes características geográficas y climáticas.

Este análisis no explica como ni por qué los seres humanos se infectan con histoplasma capsulatum pero da la medida de la variación del peligro sobre más de 3.000.000 de millas cuadradas en los Estados Unidos.

RESUME

Cet article rapporte les résultats des variations géographiques de la fréquence de la sensibilité à l'histoplasmine aux Etats-Unis. Les constatations ont pour base les tests cutanés à l'histoplasmine de 68.452 jeunes adultes, qui résidèrent toute leur vie durant dans un seul état. Les constatations faites sur ce groupe furent tirées d'observations portant sur plus de 150.000 personnes vues radiologiquement, et ayant subi des tests cutanés avec différents antigènes, selon trois programmes de recherches

simultanées, dirigées par le personnel des recherches tuberculeuses du Service de la Santé Publique.

Les tests cutanés et les interrogatoires furent obtenus, classés et interprétés d'une façon aussi uniforme que possible, pour fournir des données comparables sur une population homogène et étendue.

Une carte sommaire des Etats-Unis montre les points de plus haute fréquence, de 60 à 90% de porteurs de tests positifs dans les états centraux limités par un triangle allant de l'Ohio à l'Iowa, s'étendant au Sud—Est à travers le Missouri et l'Arkansas jusqu'à la Louisiane, avec un troisième côté allant de l'Ohio sud-ouest par le Kentucky, le Tennessee et le Mississippi.

Le taux des individus à réactions positives décroit dans l'ensemble à mesure que l'on s'éloigne de cette région triangulaire. Une région de fréquence moyennement forte, où de 30 à 60% de jeunes adultes testés eurent des réactions positives, forme un anneau grossier autour du triangle central, variant en largeur jusqu'à 300 miles. Ensuite vient un anneau de fréquence intermédiaire où l'on trouve des taux de 10 à 30% et comprenant une grande région à l'ouest. La sensibilité à l'histoplasmine était pratiquement inconnue pour les personnes ayant résidé toute leur vie dans les régions des côtes atlantique et pacifique, sauf pour quelques îles isolées où il y eut un pourcentage assez élevé.

Le projet actuel fut entrepris dans l'intention de dresser une carte de la sensibilité à l'histoplasmine de toute la nation. Une telle carte est un travail indispensable pour l'étude des facteurs qui déterminent la croissance et la diffusion de l'histoplasma capsulatum, ainsi que les conditions de sa transmission à l'homme. Avec un certain degré de précision les auteurs ont délimité les localités où l'atteinte sévit à des degrés divers alors que les conditions géographiques et climatiques étaient fort différentes. Cette analyse n'explique ni pourquoi ni comment l'homme est infecté par l'Histoplasma capsulatum mais elle détermine la variation du risque d'infection sur toute la superficie des Etats-Unis.

ZUSAMMENFASSUNG

Diese Mitteilung berichtet über die Ergebnisse einer ins Einzelne gehenden Darstellung der geographischen Unterschiede hinsichtlich des Vorkommens der Histoplasmin-Empfindlichkeit im gesamten Gebiet der Vereinigten Staaten. Das Material geht aus von den Histoplasmin-Haut-Testen an 68.452 jüngeren Erwachsenen, die Zeit ihres Lebens Bewohner der einzelen Kreise waren. Die Zahlenangahen über diese Gruppe wurden aus Beobachtungen gewonnen an mehr als 1500.000 Personen mit Röntgenuntersuchungen und Haut-Testen mit verschiedenen Antigenen aus 3 zusammenwirkenden Forschungsabteilungen unter der Leitung von Tuberkuloseforschern im öffentlichen Gesundheitsdients.

Die Hautproben und die Berichte über die Lebensgeschichte wurden so einheitlich wie möglich gewonnen, aufgezeichnet und gedeutet, um ein vergleichbares Material an einer grossen homogenen Bevölkerung zu gewinnen. Eine zusammenfassende Landkarte der Vereinigten Staaten zeigt das Gebiet der grössten Häufigkeit mit 60 bis 90% positiv ausfallenden

Reaktionen in den zentralen Bundesländern in einem Dreieck, das sich von Ohio bis Iowa erstreckt und nach Südosten ausdehnt über Missouri und Arkansas bis Louisiana, während die dritte Seite von Ohio nach Südwesten Kentucky, Tennessee und Mississippi durchquert.

Die Häufigkeit der positiven Reaktionen nimmt im Ganzen ab mit zunehmender Entfernung von Gebiet dieses Dreiecks. Ein Bezirk mässig starken Vorkommens, in dem 30-60% der jüngeren geprüften Erwachsenen positiv reagierten, bildet einen ungleichen Ring rund um das zentrale Dreieck in der Grösse von etwa 300 Meilen. Danach kommt ein Ring intermediärer Häufigkeit in der Grössenordnung von 10-30%, der ein beträchtliches Gebiet im Westen einschliesst. Eine Histoplasmin-Empfindlichkeit war praktisch unbekannt unter den lebenslänglichen Einwohnern der atlantischen und der pazifischen Küstengebiete, von verstreuten Inseln wirklich hohen Vorkommens abgesehen.

Der vorliegende Plan wurde durchgeführt in der Absicht, eine das ganze Land umfassende Karte der Histoplasmin-Empfindlichkeit zu erhalten. Eine solche Karte ist ein Erfordernis für Untersuchungen der das Wachstum und die Ausbreitung von H. kapsulatum bestimmenden Faktoren und der Bedingungen seiner Übertragung auf den Menschen.

Mit einem gewissen Grad von Präzision sind die Örtlichkeiten des verschiedenen Risikos über das gesamte Gebiet der Staaten mit abweichenden geographischen und klimatischen Bedingungen bestimmt worden. Diese Analyse erklärt weder, warum, noch wie der Mensch mit Histoplasma kapsulatum infiziert wird, jedoch misst sie die Unterschiede im Infektionsrisiko in dem 3 Millionen Quadratmeilen grossen Gebiet der Vereinigten Staaten.

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The Prognosis of Bilateral Symmetrical Diffuse Nodular Pulmonary Tuberculosis and Its Possible Relationship to Intestinal Tuberculosis*, **

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A retrospective analysis has recently been made of 1504 patients with active advanced pulmonary tuberculosis admitted to Trudeau Sanatorium 1930-1939 and followed to death or 1953-1954 in over 90 per cent.[1] These patients were rather select, not only from a socio-economic viewpoint, but those with major nontuberculous complications—advanced emphysema, cardiac decompensation, diabetes mellitus, malignancy, bronchial asthma and silicosis—and major tuberculous complications—bone and joint, genito-urinary, peritonitis or miliary—were excluded.

During an analysis of 25 years experience with a routine admission barium motor meal in search of intestinal tuberculosis, a possible relationship between the type and distribution of pulmonary tuberculous lesions and the presence of intestinal tuberculosis was suggested.[2] As a consequence, for this purpose, during the study of advanced pulmonary tuberculosis, the cases were classified in two additional ways:

1. Presence or absence on admission of bilateral symmetrical nodular distribution of the abnormal roentgenographic pulmonary shadows.[3] To be so classified there must have been diffuse finely nodular shadows, most intense at the apices, gradually disappearing toward the bases and approximately equal in distribution and in intensity in the two lungs. While this picture approximates that of miliary tuberculosis, the two conditions are readily distinguished on both clinical and roentgenographic grounds. An example of the type of case being discussed is shown in Figure 1.

2. Presence or absence on admission of roentgenographic evidence of intestinal tuberculosis. For 25 years, between 1924 and 1949, about 98 per cent of patients admitted to Trudeau Sanatorium had a routine barium motor meal regardless of the pulmonary findings. Evidence of multiple areas of obstruction, rapid passage of barium through the terminal ileum and cecum, and deformity, spasm and frank ulceration of the terminal ileum and cecum were sought.

There were 1504 patients on whom the 20 year morbidity and mortality statistics were available; "five year results" were available on 1429. The five year result was considered "good" if the disease had become clinically controlled with no evidence of cavity and with negative sputum bacteriology within three years and if relapse had not occurred within the balance of

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the first five year period. If a patient was lost through death from non-tuberculous causes or loss of contact in less than five years, the case was rated "non-evaluable." Otherwise the result was "poor." Sixty-seven patients with moderately advanced and eight with far advanced disease were "non-evaluable," leaving 1429 cases for analysis by this method. The 20 year tuberculosis morbidity and mortality, corrected for differences in duration of observation, includes all available data and hence is considered somewhat more reliable than the five year results. Patients were regarded as "sick" during a year if under treatment for active tuberculosis for six months or more of that year. A more detailed description of the materials and methods is available elsewhere.[1]

Results

From Table I it is evident that intestinal tuberculosis coincided with bilateral symmetrical diffuse nodular pulmonary tuberculosis much more (S*) frequently (43.2 per cent) than with the much more common and characteristic distributions of pulmonary tuberculous shadows (7.2 per cent).

Viewed from the other point of view, of 118 patients with intestinal tuberculosis, 19 (16.1 per cent) were found to have bilateral symmetrical diffuse nodular distribution of pulmonary shadows, while of 1311 patients without intestinal tuberculosis only 25 (1.9 per cent) had pulmonary tuberculosis of this distribution, again a considerable (S*) difference.

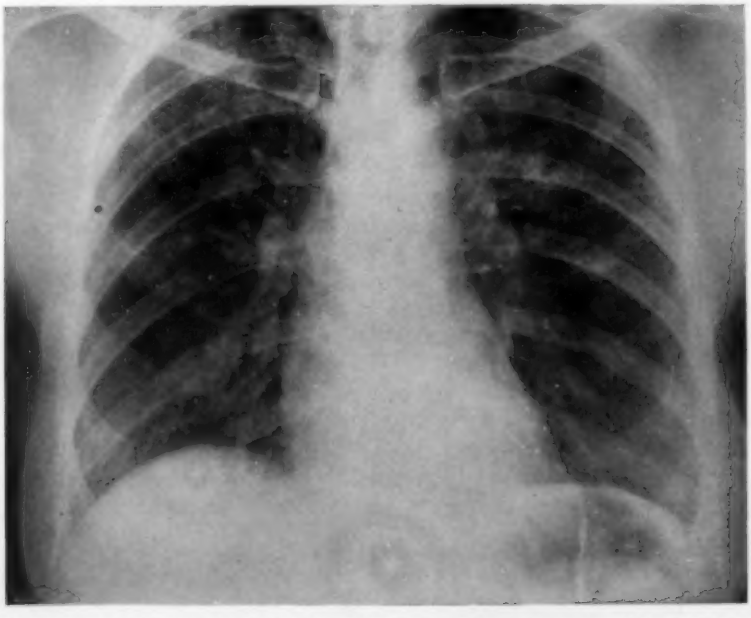

FIGURE 1: An example of the bilateral diffuse nodular pulmonary tuberculosis being discussed.

TABLE I
INCIDENCE OF INTESTINAL TUBERCULOSIS BY TYPE AND DISTRIBUTION OF PULMONARY INFILTRATION IN 1429 CONSECUTIVE ADMISSIONS WITH ADVANCED PULMONARY TUBERCULOSIS

Bilateral Symmetrical Diffuse Nodular Pulmonary Tuberculosis	Total Cases	Intestinal Tuberculosis Found	
		No.	Per Cent
Yes	44	19	43.2
No	1385	99	7.2
Total	1429	118	11.1

The five year results in patients with bilateral diffuse nodular pulmonary tuberculosis with and without intestinal tuberculosis are shown in Table II.

Patients with intestinal tuberculosis fared only slightly less favorably (NS) than those without this complication. Patients with bilateral symmetrical diffuse nodular pulmonary tuberculosis fared less well (S*) than those with other distributions of their pulmonary lesions, the difference being greater (NS) in the absence of intestinal lesions.

About one-third of patients with bilateral symmetrical diffuse nodular disease had far advanced pulmonary disease while less than one-fourth of the patients with other distributions of disease were so classified. In Figure 2 the 20 year tuberculosis morbidity and mortality experience is presented; all 1504 patients were subdivided not only by the type of

TABLE II
FIVE YEAR RESULTS OF ADVANCED PULMONARY TUBERCULOSIS BY TYPE AND DISTRIBUTION OF PULMONARY INFILTRATION AND PRESENCE OF INTESTINAL TUBERCULOSIS ON ADMISSION

Intestinal Tuberculosis Found	Bilateral Symmetrical Diffuse Nodular Distribution			Other			All		
		Poor Results			Poor Results			Poor Results	
	Total	No.	Per Cent	Total	No.	Per Cent	Total	No.	Per Cent
Yes	19	12	63.2	99	50	50.5	118	62	52.5
No	25	17	69.0	1286	576	44.8	1311	593	45.2
All	44	29	65.9	1385	626	45.2	1429	655	45.8

distribution of pulmonary lesions but also by extent of pulmonary disease (National Tuberculosis Association classification 1950). Patients were not subdivided by the presence of intestinal tuberculosis because of the findings in Table II. The increased (S*) morbidity and mortality in patients with bilateral symmetrical diffuse nodular distribution is obvious.

Comment

The pathogenesis of intestinal tuberculosis is not clearly established. It has been postulated that *M. tuberculosis* are swallowed and infect first the terminal ileum and cecum because this is the first area of delay

*S—Statistically significant, a difference which might have arisen from chance alone in no more than 2 per cent of cases. All differences which failed to meet this criterion were rated as non-significant (NS) even though in many instances they may have been indicative of possible or even likely interdependence of the developments being tested.

in passage of the fecal stream. Brown and Sampson[4] quote Fischer (1884) as "always" finding tubercle bacilli in the thoracic duct of patients with intestinal tuberculosis. Klebs[5] quotes Astley, Cooper and Ponfick as describing spread of tuberculosis from intestines and mesenteric nodes to the general circulation via the thoracic duct. Others believe this occurs[6, 7] on this basis. It has been postulated further that *M. tuberculosis* gets into the intestinal lymph channels and thence via the thoracic duct into the lungs via the superior vena cava. If the latter sequence of events does occur, and if a bilateral symmetrical diffuse nodular distribution of tuberculosis is usually a manifestation of hematogenous (non-miliary) dissemination,[8] then there should be a frequent coexistence of intestinal tuberculosis and this type of pulmonary tuberculous distribution. It appears from this retrospective analysis that such a correlation does exist.

SUMMARY AND CONCLUSIONS

1. One thousand five hundred and four rather select patients were admitted to Trudeau Sanatorium between 1930 and 1939 with advanced active pulmonary tuberculosis without major tuberculous and nontuberculous complications. The annual status for the next 15 to 25 years was determined with loss of contact in less than 10 per cent.

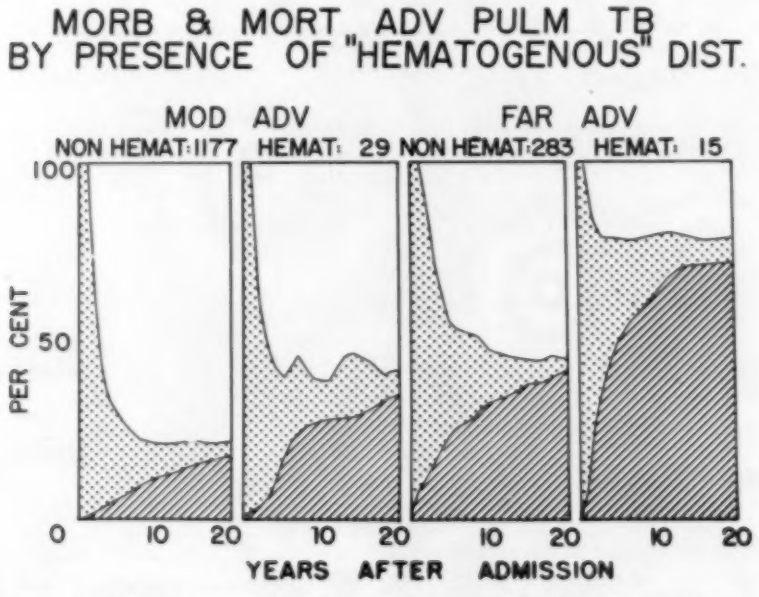

FIGURE 2: Twenty year tuberculosis morbidity and mortality experience of 1504 consecutive patients admitted to Trudeau Sanatorium 1930-1939 with active advanced pulmonary tuberculosis without major complications: by extent of disease and presence of "Hematogenous" (i.e., bilateral symmetrical diffuse nodular) distribution of lesions. (The diagonally lined space represents cumulative tuberculosis mortality, the stippled area, the proportion of survivors "sick" in each post-admission year, and the clear area, those "well.")

2. The presence or absence of intestinal tuberculosis was determined in all patients by routine barium motor meal soon after admission.

3. Pulmonary tuberculous shadows in 44 patients were characterized by a bilateral symmetrical diffuse nodular distribution; there was a significantly higher incidence of intestinal tuberculosis in these than in the patients with other distribution of disease.

4. Patients with bilateral symmetrical diffuse nodular pulmonary tuberculosis, regardless of coexistence of intestinal tuberculosis, had a much poorer long term prognosis than patients with other forms of pulmonary tuberculosis.

5. Bilateral symmetrical diffuse nodular pulmonary tuberculosis probably represents a nonmiliary hematogenous dissemination of disease, frequently originating from drainage of *M. tuberculosis* into the thoracic duct from a tuberculous intestine.

RESUMEN Y CONCLUSIONES

1. Entre los años de 1930 y 1939 ingresaron 1504 enfermos seleccionados sin complicaciones mayores tuberculosas o no tuberculosas, en el Sanatorio Trudeau. Sus condiciones de salud anualmente se pudieron determinar por 15 a 20 años con una pérdida de contacto de menos de 10 por ciento.

2. La presencia o ausencia de tuberculosis intestinal se determinó en todos los enfermos por el examen rutinario del tránsito de la comida de bario pronto después de su entrada.

3. Las manchas de la tuberculosis pulmonar se caracterizaron en 44 enfermos por una distribución sumétrica, bilateral difusa; hubo una frecuencia mayor de tuberculosis intestinal en esta forma que en los enfermos con otro tipo de distribución.

4. Los enfermos con una tuberculosis bilateral nodular difusa simétrica, sin tener en cuenta la coexistencia con la tuberculosis intestinal tuvieron un pronóstico a largo plazo más malo que los que tenían otras formas.

5. La tuberculosis pulmonar difusa, simétrica nodular probablemente representa una diseminación hematógena no miliar de la enfermedad que es originada, por la entrada del bacilo de la tuberculosis en el conducto torácico a partir del intestino tuberculoso.

RESUME

1. 1504 malades choisis ont été admis au Sanatorium Trudeau entre 1930 et 1939 alors qu'ils étaient atteints de tuberculose pulmonaire évolutive grave sans complications majeures, tuberculeuses ou non. Le bilan annuel pour les 15 à 25 années suivantes a été effectué avec moins de 10% de malades perdus de vue.

2. L'existence ou non d'une tuberculose intestinale a été déterminée chez tous les malades, après ingestion d'un repas baryté tout de suite après leur admission.

3. Les manifestations radiologiques de tuberculose pulmonaire chez 44 malades avaient les caractéristiques d'ombres bilatérales symétriques à forme nodulaire. Il y eut un pourcentage éloquemment plus élevé de tu-

berculose intestinale chez ces malades que chez ceux qui présentaient une autre forme de la maladie.

4. Sans prendre en considération l'association de tuberculose intestinale, les malades atteints de tuberculose pulmonaire à forme nodulaire diffuse et à localisation bilatérale symétrique, eurent une évolution fatale beaucoup plus rapide que les malades atteints d'autres formes de tuberculose pulmonaire.

5. La tuberculose pulmonaire à forme nodulaire diffuse et à localisation bilatérale symétrique représente probablement une dissémination hématogène non miliaire de la maladie, résultant fréquemment de la pénétration des bacilles tuberculeux dans le thorax à partir d'un intestin infecté.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

1. 1504 ziemlich ausgewählte Kranke wurden in das Trudeau Sanatorium eingewiesen zwischen 1930 und 1939 mit fortgeschrittener aktiver Lungentuberkulose ohne beträchtliche tuberkulöse und nicht tuberkulöse Komplikationen. Der jährliche Status für die nächsten 10-25 Jahre wurde bestimmt mit einem Verlust der Verbindung in weniger als 10%.

2. Das Vorliegen oder Fehlen einer Darm-Tuberkulose wurde bei allen Kranken kurz nach der Aufnahme bestimmt mittels planmässiger Barium-Bewegungsmahlzeit.

3. Pulmonale tuberkulöse Verschattungen bei 44 Kranken waren gekennzeichnet durch ihre bilaterale symmetrische diffuse knotenförmige Verteilung; es bestand ein Signifikant höheres Vorkommen von Darmtuberkulose bei ihnen im Vergleich zu den Kranken mit anderen Ausbreitungsformen.

4. Kranke mit beidseitiger symmetrischer diffuse knotenförmiger Lungentuberkulose hatten unberücksichtigt des gleichzeitigen Vorkommens von Darmtuberkulose auf lange Sicht gesehen eine viel schlechtere Prognose als Kranke mit anderen Formen von Lungentuberkulose.

5. Eine beidseitige symmetrische diffuse knotenförmige Lungentuberkulose stellt wahrscheinlich eine nicht miliare haematogene Krankheitsausbreitung dar, die häufig ausgeht von einer Ableitung von *M. tuberculosis* aus einem tuberkulösen Intestinum in den ductus thoracicus.

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Liver Biopsy in a Tuberculosis Hospital

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Histologic examination of liver tissue obtained by needle biopsy has vastly improved knowledge of hepatic diseases and of systemic diseases with hepatic involvement. In addition, liver biopsy has become a valuable tool in solving difficult clinical diagnostic problems.

Diagnosis of tuberculosis has been established by means of liver biopsy on numerous occasions.[1-4] The extent of hepatic involvement in pulmonary tuberculosis has been studied from post mortem material[5] and recently from specimens obtained by needle biopsy.[6] To determine the value of liver biopsy in a tuberculosis hospital the results of biopsies on 128 patients were reviewed.

Materials and Methods

All patients studied were under observation and/or treatment for tuberculosis at the Oak Forest Tuberculosis Hospital. The average age of the patients studied was 40 years. The youngest was 15 and the oldest 77 years. Ninety-five men and 33 women were studied. In general, the reason for selection of patients for liver biopsy could be divided into six groups:

1. Possible miliary tuberculosis in 32 patients.
2. Pleural effusion in 13.
3. Extra-pulmonary tuberculosis in 22.
4. Specific diagnostic problem in 32.
5. Possible amyloidosis in 8.
6. Effects of drug therapy in 21.

The possible miliary group consisted of those clinically suspected of having miliary tuberculosis on the basis of characteristic diffuse nodular lesions on chest x-ray films. Some had tubercle bacilli cultured from bone marrow, and one had extensive cavitary lesions on x-ray film. Biopsy was performed as early as possible, but several had been on treatment for as long as four months prior to biopsy. Patients with pleural effusion were studied in an attempt to prove etiology. Those with extra-pulmonary tuberculosis had positive lymph node biopsies, bone lesions, ischiorectal abscesses, genitourinary tuberculosis, peritoneal, pericardial, or meningeal lesions. The specific diagnostic group consisted of cases in whom cirrhosis was suspected because of abnormal results of liver function tests or with unexplained hepatomegaly. When amyloidosis

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was suspected clinically, a Congo red test and liver biopsy were performed. The last group consists of patients with abnormal results of liver function tests encountered during the course of evaluation of isonicotinic acid hydrazide treatment. These abnormal results raised the possibility of liver damage from the drug, and liver biopsy was performed to further investigate this possibility. Some overlapped into more than one group but were placed under the heading considered most appropriate.

Prothrombin time of 75 per cent of normal or better was required before the biopsy was performed.

During the first half of this study the Silverman needle[7] was used. In the latter half the needle designed by Terry[8] was employed because larger specimens were obtained.

The specimens of liver tissue were fixed in Zenker-formalin solution, cut at four microns, and a single section was stained with hematoxylin and eosin according to established technics. In addition, Mallory's trichrome stain and periodic acid Schiff stains were used in some instances. A series of biochemical determinations, including serum albumin, globulin, tubidometric gamma globulin,[19] cholesterol-cephalin flocculation, thymol turbidity, and alkaline phosphatase were done.

Results

Histologic lesions found were divided into five categories: (1) miliary granulomas; (2) histiocytic nodules; (3) non-specific reactive hepatitis; (4) amyloid infiltration; and (5) non-tuberculous lesions.

The tuberculous granulomas consisted of accumulations of epithelioid cells usually surrounded by a lymphocytic ring. Some Langhans' type giant cells were present and in some cases central caseation was noted

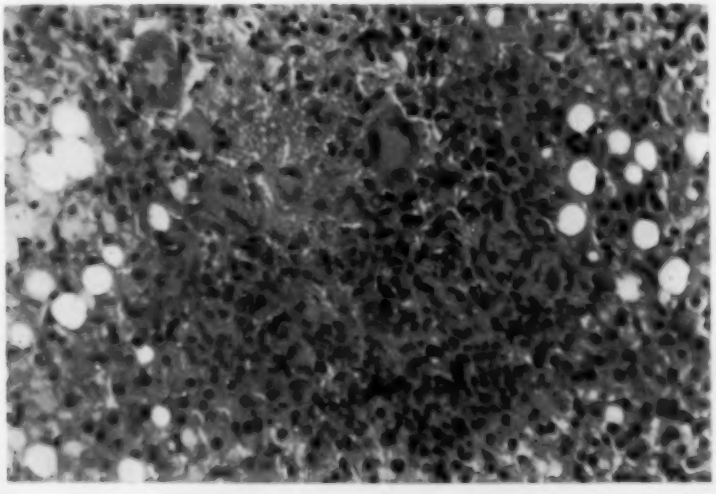

FIGURE 1: Miliary granuloma with central caseation and Langhans giant cells in a liver biopsy specimen from a patient with a clinical picture of miliary tuberculosis. Hematoxylin and eosin. (X190)

(Fig. 1). Tubercles were usually distributed throughout the lobule, but were often seen near the central vein. Tuberculous etiology is suggested by this histologic picture, but cannot be proved on this basis alone. Absolute differentiation from sarcoid follicles cannot be made unless tubercle bacilli are demonstrated by specific staining or culture.

Histiocytic nodules are represented by accumulation of histiocytes apparently differing from Kupffer cells. These endothelial cells resemble epithelioid cells, but as a rule are not as large. Lymphocytes were occasionally found in the nodules. The entire histiocytic nodule is smaller than the tuberculous granuloma and central caseation is not seen. These nodules are strongly suspicious of tuberculous etiology, but are weaker evidence than the tuberculous granuloma described above. In some instances histiocytic nodules were associated with some of the changes described below as non-specific reactive hepatitis (Fig. 2).

Non-specific reactive hepatitis is represented by focal or diffuse degenerative changes of the liver cells, focal necrosis, focal regeneration, Kupffer cell mobilization, and portal and perioportal cellular infiltration (Fig. 3). These histiologic features vary in intensity and extent in the individual patient. In some instances all of the above changes are present and extensive, and in others only a few of the changes are noted. The extent and severity of histological changes was roughly proportioned to clinical toxicity.

Amyloid changes consisted of deposition of characteristic amyloid material throughout the lobule in varying amounts.

Eight patients were clinically suspected of having secondary amyloidosis.

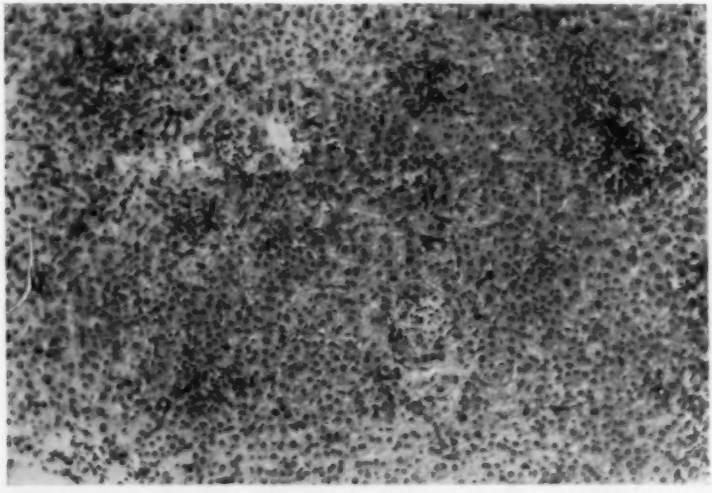

FIGURE 2: Histiocytic nodule composed of endothelial cells and lymphocytes in a liver biopsy specimen from a patient with far advanced pulmonary tuberculosis. Note also the increase in number and size of the Kupffer cells and the increased cellularity of the portal triads characteristic of non-specific reactive hepatitis. Hematoxylin and eosin. (X95)

Four of these showed extensive amyloid infiltration in the liver (Fig. 4). One with histologic amyloid infiltration had a normal Congo red test. Two who did not have histologic amyloid infiltration had complete removal of Congo red from the serum in one hour.

The non-tuberculous lesions consisted of six instances of fatty infiltration with beginning cirrhosis formation; two cases of viral hepatitis

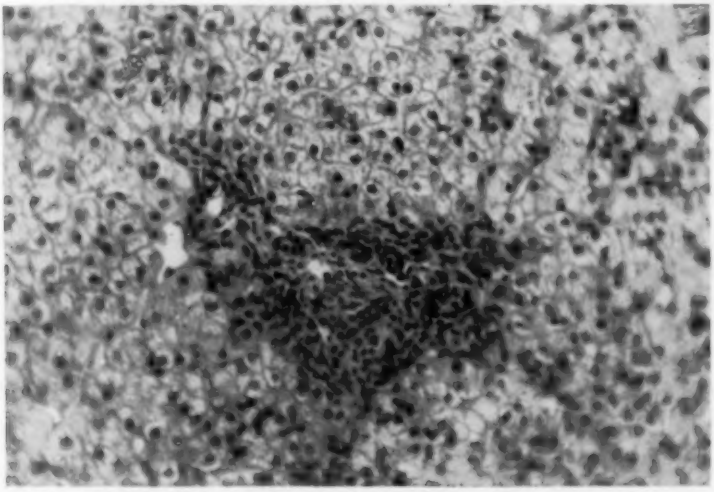

FIGURE 3: Portal and periportal infiltration with lymphocytes and histiocytes in a liver biopsy specimen from a patient with far advanced pulmonary tuberculosis. Hematoxylin and eosin. (X190)

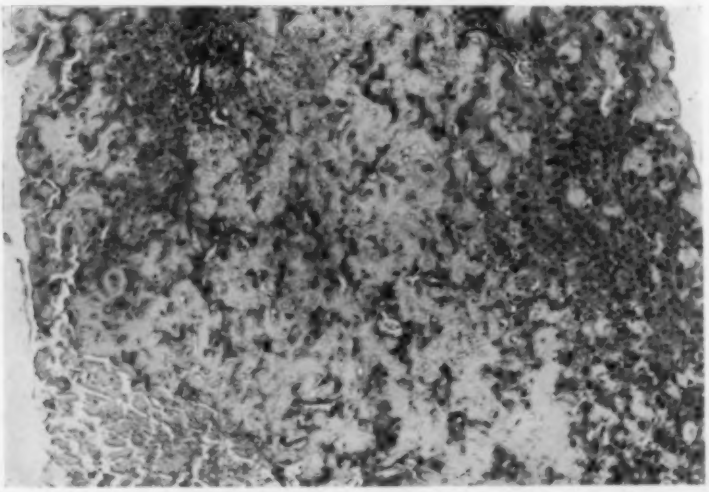

FIGURE 4: Amyloid deposition in a liver biopsy specimen from a patient with far advanced pulmonary tuberculosis and tuberculous osteomyelitis of the femur. Hematoxylin and eosin. (X85)

and one each of hemochromatosis, myeloid metaplasia, lymphoma and sarcoidosis (Fig. 5).

The most frequently seen lesion was non-specific reactive hepatitis (44 per cent). Next in order of frequency were histiocytic nodules (20 per cent); tuberculous granuloma (19 per cent); specific non-tuberculous lesions (10 per cent); amyloid infiltration (4 per cent); and normal liver (3 per cent). The distribution of histological lesions for each clinical reason for biopsy is presented in Table I.

TABLE I
REASON FOR BIOPSY AND HISTOLOGICAL FINDINGS IN 128 CASES OF TUBERCULOSIS

		Histological Diagnosis					
Reason for Biopsy	No. of Cases	Tuberculous Granuloma	Histiocytic Nodules	Non-Specific Reactive Hepatitis	Amyloid	Normal	Other
		Per Cent	Per Cent	Per Cent	Per Cent		
Possible Miliary TBC	32	34	16	46	0	0	3
Pleural Effusion	13	15	23	46	0	15	0
Extra-Pulmonary TBC	22	40	23	36	0	0	0
Diagnostic	32	3	18	37	0	6	34
Possible Amyloid	8	0	12	25	63	0	0
Evaluation % Drug Effect	21	0	19	71	0	0	0
		23%	26%	58%	5%	4%	12%

FIGURE 5: Partially hyalinized follicle of sarcoidosis in a liver biopsy specimen from a patient with diffuse nodular shadows seen in a chest x-ray film. Hematoxylin and eosin. (X190)

Table II contains the clinical reason for biopsy and extent of pulmonary and extra-pulmonary tuberculosis in each of the 23 cases in which tuberculous granuloma were found.

Table III represents the correlation between the histological diagnosis and the abnormal blood chemistry determinations.

Discussion

The primary objective of this study was to demonstrate the practical value of needle biopsy of the liver in the management of tuberculosis. Tuberculous granulomas in liver tissue means hematogenous dissemination, at least to the liver. Some patients presented the clinical and roentgenologic picture of acute miliary tuberculosis, while others did not. Still others had clinical and roentgenologic evidence of acute miliary tuberculosis, but no tuberculous granuloma was found. Failure to find granulomas may be due to uneven distribution or fewer granulomas, or it may be due to failure to make serial sections of the entire biopsy specimens. The amount of liver tissue obtained is small in comparison to the size of the liver, and tuberculous granulomas may be present in the liver even though not seen on a single section of the biopsy.

Tuberculous granulomas are not necessarily diagnostic of acute miliary tuberculosis, but are frequently seen in extra-pulmonary tuberculosis and tuberculous pleural effusion. From a clinical standpoint, the demonstration of tuberculous granulomas is significant regardless of the diagnosis before biopsy. In some instances of pleural effusion, this was the only laboratory proof of tuberculosis. Some cases of tuberculous lymphadenopathy might not have been adequately treated unless the extent of the tuberculous process had been demonstrated by liver biopsy.

The findings of non-specific reactive hepatitis solved many puzzling clinical and biochemical problems. In several patients a clinical diagnosis of cirrhosis was made but non-specific reactive hepatitis was found. This lesion probably represents a hepatic reaction to tissue breakdown or some other endogenous toxin. The possibility of liver damage from

TABLE II
CLINICAL DATA IN 23 PATIENTS WITH TUBERCULOUS GRANULOMAS OF THE LIVER

		Pulmonary Tuberculosis					Extrapulmonary Tuberculosis							
Reason for Biopsy	No. of Cases	Minimal	Moderately Advanced	Far Advanced	Diffuse Nodules	Pleural Effusion	Lymph Nodes	Peritonitis	Bone	Kidney	Genital	Pericardium	Meningitis	Rectum
Miliary TBC	11	1	0	2	8	1	1	1	1	0	0	0	0	0
Pleural Effusion	2	0	1	1	0	2	0	0	0	0	0	0	1	0
Extrapulmonary Tuberculosis	9	2	1	2	0	2	3	2	3	1	1	1	1	2
Hepatomegaly	1	0	1	0	0	0	0	0	0	0	0	0	0	0

TABLE III
CORRELATION OF BIOCHEMICAL AND HISTOLOGICAL FINDINGS

Histologic Findings	No. of Cases	Per Cent Abnormal Results With Various Tests						
		Albumin	Globulin	Gamma Globulin	Cephalin Flocculation	Thymol Turbidity	Low Total Cholesterol	Alkaline Phosphatase
		Percentages						
Tuberculous Granuloma	19	31	58	74	15	15	31	0
Histiocytic Nodules	24	8	21	62	11	0	16	8
Non-specific Reactive Hepatitis	54	20	32	64	10	5	22	2
Amyloidosis	2	0	100	100	0	0	0	0
Non-tuberculous Lesions	6	50	66	66	16	0	66	0

isonicotinic acid hydrazide arose, but non-specific reactive hepatitis was found to account for the clinical and biochemical abnormalities. The severity of the hepatic changes roughly mirrored the systemic toxicity of the disease, and in some patients on isonicotinic acid hydrazide serial biopsies revealed improvement in the histologic appearance.

Liver biopsy proved valuable in establishing the diagnosis of beginning cirrhosis or healing hepatitis, as well as the isolated cases of hemochromatosis, myeloid metaplasia, lymphoma, and sarcoidosis. Each of these patients presented a clinical diagnostic problem that was solved by liver biopsy.

A disparity between the Congo red test and the histological demonstration of amyloid deposition occurred in patients with amyloidosis. Some had abnormal Congo red removal, but no amyloid infiltration was seen. this may mean that the liver is not uniformly involved in secondary amyloidosis.

It was not possible to predict the histologic diagnosis from biochemical abnormalities. These tests are of distinct value in the study of pulmonary tuberculosis but can not be used as a substitute for liver histologic examination. Elevated gamma globulin was the most frequently demonstrated abnormality and the group with tuberculous granulomas had the highest over-all incidence of abnormalities. This had previously been related both to changes in the liver and to the number of plasma cells in bone marrow.[10] Results of the other hepatic tests were not correlated with either clinical findings or with histologic alterations.

SUMMARY

The practical value of liver biopsy in a tuberculosis hospital was found to be:

1. Hematogenous dissemination with or without the clinical features of miliary tuberculosis is recognized. Hepatic dissemination does not neces-

sarily imply generalized miliary tuberculosis which therefore cannot be diagnosed from the liver biopsy specimen alone. Recognition of dissemination is important for prognosis and therapy in pulmonary tuberculosis and more so in extra-pulmonary forms.

2. The degree of non-specific reactive hepatitis (liver damage, focal necrosis and inflammation) reflects systemic toxicity.

3. Frequently associated diseases such as cirrhosis or hepatitis are detected.

4. The presence and extent of amyloid deposition can be evaluated more effectively than with Congo red tests alone.

RESUMEN

El valor práctico de la biopsia del hígado en un hospital de tuberculosos se encontró ser:

1. La diseminación hematógena con o sin las características clínicas de la tuberculosis miliar, se reconoce.

La diseminación hepática no implica necesariamente la tuberculosis miliar generalizada la cual no puede ser diagnosticada solamente por el espécimen de la biopsía de hígado.

El reconocimiento de la diseminación es importante para el pronóstico y el tratamiento de la tuberculosis pulmonar y más aún para la extrapulmonar.

2. El grado de hepatitis reactive no específica (daño hepático, necrosis focal e inflamación) refleja la toxicidad general.

3. Frecuentemente se descubren afecciones asociadas tales como la cirrosis y la hepatitis.

4. La presencia y la extensión de los depósitos amiloides puede apreciarse mejor que con la prueba del Congo Rojo sola.

RESUME

Les auteurs démontrent la valeur pratique de la biopsie du foie dans un hôpital pour tuberculeux:

1. Elle permet de reconnaitre la dissémination hématogène avec ou sans les caractéristiques cliniques de la tuberculose miliaire. La dissémination hépatique n'implique pas forcément la tuberculose miliaire généralisée, qui ne peut être diagnostiquée sur la seule biopsie du foie. La constatation de la dissémination est importante pour le pronostic et la thérapeutique en tuberculose pulmonaire et plus encore dans les formes extrapulmonaires.

2. Le degré d'une réaction hépatique non spécifique (lésions du foie, foyer de nécrose, et inflammation) reflète une atteinte toxique de ce viscère.

3. Des maladies fréquemment associées, telles que cirrhose et hépatite peuvent être mises en évidence.

4. La présence et l'extension d'une dégénérescence amyloïde peuvent être évaluées avec plus d'efficacité que par les ceuls tests au rouge Congo.

ZUSAMMENFASSUNG

Der praktische Wert einer Leber-Biopsie in einem Tuberkulose-Krankenhaus ergab sich in folgendem:

1. Eine haematogene Aussaat mit oder ohne die klinischen Merkmale der Miliar-Tuberkulose wird erkannt. Eine Aussaat in der Leber schliesst nicht notwendig eine generalisierte Miliartuberkulose ein, die daher nicht aus dem Leberpunktionspräparat allein diagnostiziert werden kann. Die Feststellung einer Dissemination ist wichtig für die Prognose und Therapie bei Lungentuberkulose und noch weit mehr bei den extrapulmonalen Formen.

2. Der Grad der unspezifischen reaktiven Hepatitis (Leberschaden, Herdnecrose und Entzündung) spiegelt die allgemeine Toxizität wieder.

3. Oft werden Begleitkrankheiten wie Zirrhose oder Hepatitis entdeckt.

4. Das Vorliegen und das Ausmass einer Amyloid-Ablagerung kann wirksamer abgeschätzt werden als mit Congorotproben allein.

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Editorial

The First Line of Defense in Tuberculosis—The Practicing Physician

In many areas of the world, especially in the Western World, tuberculosis is rapidy coming under control. It seems possible that the goal of wiping it out completely can be reached many years hence. It will require several generations if we adopt the same concept for human beings that we now maintain in our certified cattle herds where the only allowable standard is a fraction of one per cent of positive reactors to tuberculin.

Whole new methods of approach are now available. We can combine well-known facts and well-tested procedures and implement these with recently developed therapeutic measures. Wide-spread acceptance of these ideas is occurring at the specialist's level, as more sustaining facts are resulting from current research. There is also a great surge of renewed interest in tuberculosis as a disease among the general practitioners of medicine. These include not only the family doctor, but the pediatrician, the internist, even the obstetrician and some other allied groups. These physicians now have available to them methods of diagnosis and treatment that they themselves can use, that they can apply to their own patients' benefit. Let us briefly review this development.

When Koch described tuberculin in 1890 he had no concept of its present use. It was developed by him as a means of treating tuberculosis. The idea of allergy was conceived by Pirquet in 1906. He described using tuberculin for the purpose of determining which persons were infected with tubercle bacilli. It has been clearly demonstrated over the years that only those persons who are infected with tubercle bacilli to the extent that there is tubercle formation will give a positive tuberculin reaction. We are indebted to Carroll Palmer and his associates for their conception of the tuberculin unit—one unit being 0.00002 mg. of reference standard PPD or 0.01 mg. of international standard Old Tuberculin. Their contribution has been most helpful.

The intracutaneous tuberculin test, properly done with a potent solution, is one of our most reliable biologic testing procedures. The experimental error in Mantoux testing has been studied and is indeed small.

Of the different methods that are in use, the patch test gives only approximately 70 per cent reliability. Various percutaneous tests with ointments, the flour-paper-jelly types and their modifications have all been shown to be difficult to read and hard to evaluate. The Heaf multiple puncture test is having considerable vogue in Britain. None of these latter mentioned methods can be recommended.

The tuberculin test becomes even more important in differentiating those persons who are truly infected with tubercle bacilli from those who are not. Palmer, from his experience in the United States Public Health

Service and the World Health Organization, states that almost universally the use of five tuberculin units (defined above), and in the Northern part of the United States at least not more than 10 tuberculin units, will differentiate between those persons infected with tubercle bacilli and those who are not.

Positive tuberculin tests pinpoint those individuals comprising the group in which new active cases of tuberculosis will develop. Discovery of a recent conversion from a negative to a positive reaction means that there is a known or unknown source of tuberculosis in the converter's environment. This is the only test that will actually tell us which persons are infected, in contrast to x-ray or sputum examination, for example, which may delineate those who, under the old concept, have clinical disease. Tuberculin testing is important as a case finding method in areas of low incidence of tuberculosis. In areas of high incidence, though its value as a general case finding method may be less, it becomes important to the individual as a diagnostic measure. Simple tuberculin testing in any area effectively evaluates the progress made in the application of other well-known epidemiological procedures.

The pathology of tuberculosis has recently been discussed in detail by Edgar Medlar. Reviewing his life-time work as a pathologist in this field, Medlar emphasizes that progressive pulmonary tuberculosis is initiated by a microscopic form of lobular pneumonia. Without an appreciation of the prolonged time-sequence of events between this initial microscopic focus of infection and the discovery of "clinically significant" disease, the problem presented by the tuberculosis patient can hardly be properly evaluated.

Before the 1920's almost the only kind of pulmonary tuberculosis that the physician actually had to deal with was far-advanced disease. Moderately advanced disease was recognized with difficulty, and minimal disease not at all. It was not until the advent of improved x-ray technique and the introduction of the celluloid film that the concept of minimal disease was at all realized. It took at least 10 years—into the early 1930's—before the mechanism of the development of minimal pulmonary disease was clearly perceived. Then came case finding by the mass x-ray method initiated by Manoel de Abreu. This posed new and different problems. We have come a long way, since those earliest days, in understanding the development of early tuberculous infection and the progress of this disease in the infected persons.

J. Arthur Myers correctly states that, after tuberculin was produced by Koch and methods for its use as a skin test were devised by Pirquet and Mantoux, wrong concepts resulted from testing many persons and finding that most of the positive reactors appeared to be in good health. The usual clinical examination revealed no evidence of disease. It was felt, therefore, that those who reacted to tuberculin but had no symptoms, and in whom lesions were not demonstrable otherwise, had infection without disease, whereas the reactor with symptoms and/or demonstrable lesions had "clinical tuberculosis." Thus a sharp dividing line was imagined to exist between infection and disease. Myers goes on to state that, with the

advent of the x-ray film, it was thought that only those who had shadow-casting lesions had pulmonary disease, and that those who reacted to tuberculin but had clear x-ray films, and no other demonstrable lesions, had infection but no disease.

Ghon clarified this situation in the second decade of this century by meticulous necropsies on the bodies of 184 persons who during life had no evidence of tuberculosis except a positive tuberculin reaction. He found tuberculous lesions in all of these bodies. We have come to realize that there are always many more lesions in the lung than the x-ray shows. During resectional surgery this has become a common finding.

Myers goes on to describe his work with medical students. At first, attention was directed toward those students who had gross lesions. In the graduating classes of 1919 to 1932 at the University of Minnesota Medical School, demonstrable lesions on the x-ray film appeared in 92, and 11 of these died. After tuberculin testing of all medical students became routine in 1928, all who had a positive reaction on entrance, as well as those who converted, were identified and watched carefully. In the classes graduating from 1930 to 1942, approximately 40 per cent of those who entered with negative tuberculins converted while in school. This was reduced to 11 per cent in the classes of 1943 to 1949, and to 8 per cent from 1949 to 1953. During the past 12 years only one student developed a pulmonary lesion that could be detected on the x-ray film.

Let us turn to another infectious disease—typhoid fever. When typhoid fever was a common disease, the use of epidemiological methods in controlling the milk and water supply and the isolation of individual cases resulted in a marked drop in the incidence of that disease. But this drop reached only a certain level and then continued at that level. The use of these methods alone dropped it no further. It was not until each individual case of typhoid fever was traced to its source, all the contacts of that patient examined, and the source itself controlled, that the rate dropped sufficiently so that now it is practically a non-existent disease in much of the Western world.

In the field of tuberculosis we may have reached, in some areas, the point of diminishing returns from the use of our present epidemiological methods alone, and possibly we should adopt another point of view. That point of view might be that, when an individual converts from a negative to a positive tuberculin, the disease tuberculosis begins. James Waring in 1951 recognized that tuberculous infection means the beginning of disease, which all too frequently becomes serious if not fatal. He states that we should give earnest consideration to the treatment of tuberculosis with chemotherapy at the earliest possible moment, just as we have done with syphilis.

Up to the advent of modern chemotherapy, much of this would have been wishful thinking. Actually, it was the advent of isonicotinic acid hydrazide that made possible the practical application of these concepts.

Myers also states that, as long as we allow primary infection to go unnoticed and begin treatment only after illness appears or after lesions are

demonstrable by x-ray, we can hardly expect to cure tuberculosis in the strict sense of the word. When tubercle bacilli find their way into the human body and allergy develops, these bacilli are focalized in various places, resulting in tubercle formations. At one or more of these points of focalization, sooner or later clinical lesions may appear. More lesions usually develop in the lungs because original focalizations occur there with greater frequency. Diagnosis can be made in most cases within six weeks after the bacilli invade the body. This diagnosis is dependent, of course, on conversion of the intracutaneous tuberculin test from negative to positive. At the time of conversion the primary lesions will be small and vascular and drugs can easily reach the tubercle bacilli they contain.

As pointed out by both Waring and Myers, when tuberculous disease is found by the tuberculin test, the earliest possible diagnosis has been made. It would seem logical, then, that the best time to treat tuberculosis is in the recent converter.

The efficacy of our present drugs is substantiated from many sources. A study by Edith Lincoln on treating primary tuberculosis in children showed that, in their pediatric service at Bellevue Hospital in New York City, the use of streptomycin plus PAS reduced the mortality among such children from 21.5 per cent to 5 per cent. Since they began to use INH in 1952, this mortality has fallen to 1.5 per cent.

The work of L. H. Schmidt in Cincinnati, most of which is unpublished, adds important information. The monkey is an extremely susceptible animal to tuberculosis. When a tuberculin-negative monkey is introduced into a monkey colony where known open tuberculosis exists, it is only a matter of weeks before the newcomer is dead of extensive disease. Giving such an animal INH prior to and during its residence in a monkey colony containing much open tuberculosis results not only in this newcomer's surviving in apparent good health, but not even a positive tuberculin skin reaction develops. This is a remarkable demonstration of the effectiveness of INH under such conditions.

Robinson, Myers and Middlebrook showed that four infants under the age of two years, who were known contacts and had negative chest x-ray films and positive skin reactions to Old Tuberculin, when treated with INH alone in a dose of 8 mg. per kilogram of body weight per day became negative to OT in a 1:100 dilution within a year. W. P. Dick of Scotland, in his study of a large series of tuberculous lesions after chemotherapy, gives a summary of the pathological changes in the lungs and kidneys to explain the reaction in the local inflammatory lesion to INH.

From the above studies, it would seem that a potent drug can reach the tubercle bacilli when the lesions are still vascular and in most cases, at this stage, it appears that the tubercle bacilli can be rendered non-infectious.

In the United States, I am told, during the past year candidates for enlistment in the Marines showed less than 10 per cent reaction to intradermal tuberculin tests. In a similar study in Navy recruits, the incidence was under 5 per cent. A recent study of high school students in an average industrial area in the West, over two successive years, showed an incidence

of positive reactors under 5 per cent.

The idea of certifying schools, based on the tuberculin reaction of the students as a test of epidemiological control, was initiated in Minnesota more than 10 years ago. The Committee on Tuberculosis of the American School Health Association was appointed in 1934, with Dr. J. Arthur Myers of Minneapolis as chairman. It was noted that, whenever good tuberculosis control methods had been operating in schools for a number of years, the mortality, morbidity, and infection rates decreased much more rapidly than in other areas. After considering numerous projects, a plan was adopted for certification of schools which would meet certain qualifications with reference to tuberculosis control. There has been great interest in this program. It is now being carried on in seven states and in certain other areas.

With this brief factual background, let us come back to the individual doctor. It is apparent that the physician in private practice has renewed his interest in the field of tuberculosis. For a good many years there was a gradually diminishing interest in tuberculosis among the men who actually look after the individual patient, and with this lack of interest there came a natural drop in their acuteness in discovering early disease and in realizing its implications. This seems to have changed—maybe due in part to the concepts as outlined above and because of the tools that every physician can now use in diagnosing and treating his own patients. It is a relatively simple matter for a physician to tuberculin test his patients and know the exact status of their skin reaction. When a recent converter is identified, a clinical examination with chest x-ray film should be done. Most of the findings will be negative—the only positive findings being the tuberculin test. Now with adequate chemotherapy it is possible, and many of us feel it is advisable, for this patient to be treated at this point. This the physician himself can do.

I in no way intend to minimize the splendid contributions that the official health agencies, the health officers, the voluntary tuberculosis associations, the university clinics, the general hospitals, and the school physicians have made in bringing tuberculosis under control to the point that we have now reached. However, it seems expedient to emphasize that the approaches which have been used in the past may now be further implemented. The possibility to make remarkable advance is within our grasp.

The renewed interest in tuberculosis and the tools now available to the men in practice—to the internist, the general practitioner, the pediatrician, etc.—are impelling them to seek information about accurate tuberculin testing, because it leads into something that is positive and objective. Any physician interested enough to find out the details can apply them. I am not speaking of the old concept of clinical disease in which there are positive x-ray film shadows, positive sputum, etc. This, I believe, requires the application of special knowledge in the use of these potent drugs and various other measures of therapy. If these latter patients are to be treated by the general man, it should be always with the continuing advice and periodic observation of someone specially trained in the disease.

At this point we are speaking of a new concept of the disease tuberculosis, that of infection demonstrated by the conversion from a negative to a positive tuberculin test — the earliest manifestation of the disease itself. This wipes out the separation between infection and clinical disease in tuberculosis and, at least for the known recent converter, makes it possible (one might say it was almost beginning to be mandatory) for us to begin treatment of the disease at this point. Fortunately, this is not complicated—it actually entails only the search for the source of infection, the removal of that source, and the treatment of the individual who is a known recent converter.

How then are we to further interest the practitioner of medicine who sees the individual patient in these facts and in including them in his armamentarium? In the medical school, yes—but this is a slow process. Over half of such students are still being taught tuberculosis today by men who do not pretend to be experts in the disease. At medical meetings, yes—but a doctor is sometimes slow to translate such knowledge into his daily practice. With the help of organizations such as the Academy of General Practice, the National Pediatrics groups, the national, state or local organizations of internists, yes. This would be very good and helpful, but also is usually slow in adoption. Shall we depend upon postgraduate medical education through the university extension and medical school reunion programs, and upon courses of the local county medical societies and the specialized groups? This would be especially helpful, with a chance for good discussion. We should use all of these methods and more.

A method that would directly aid the practicing physician with his own individual patients would indeed be helpful. Once he had used the techniques a few times and had workable personal knowledge of them, wider daily application of them would follow.

Some years ago a scheme, patterned after the fruitful work in Minneapolis, was instituted in our own area. It proved very effective. However, it became a war casualty and has but recently been revived with considerable initial success. The method is briefly as follows:

A study is set up to ascertain the tuberculin status of patients referred by private physicians to minifilm units. The referring doctor is contacted by a full-time employee, in this instance of the County Tuberculosis Association (it could be a nurse, a social worker properly instructed, or any other suitable person), and is asked for certain simple specific information regarding these patients for this study. He is usually willing to participate on such a basis. The first information requested is the tuberculin reaction. The physician thereby begins to apply tuberculin tests on his own patients. The tuberculin is furnished to him, the syringe if necessary, and a simple standard technique that has been worked out for the purposes of this study is explained. Thus, the doctor re-explores the value of this test in terms of modern thinking about tuberculosis. Very likely, having the materials and the information on present-day uses at hand, he begins to use tuberculin tests on other of his patients. This is physician education in his own office and on his own patients. He may thus develop habits that

he will continue with, much to his own personal satisfaction and for the good of his patients.

With the renewed interest of the practitioner of medicine in the application of the tuberculin test, and with the drugs now available for treatment of the known recent converter, it becomes a stimulating and exciting problem to him among his own patients.

Some of these ideas as yet cannot be completely documented in a fashion satisfying to the biostatistician. That will not really be possible for a generation or two. But here is an immediate problem at hand, where the prospects are alluring, and where the facts gathered from many sources practically all point in the same direction. This general scheme is easy to carry out and can be of wide application, certainly in an area where there is a low incidence of tuberculosis. This should not mitigate in any way the present attempts at the finding of the open case of tuberculosis, the segregation while infectious, and adequate, prompt, energetic treatment to cure the patient and render him non-infectious to his family and his associates.

We are thus returning to our first line of defense in tuberculosis—the physician who is in the private practice of medicine and who actually sees the individual patient first. With his renewed interest and having available these additional tools he himself can now apply, one can see that a whole new vista has been opened for him which may go far in controlling the development among his own patients of what we now call clinical disease.

HAROLD GUYON TRIMBLE, M.D., F.C.C.P.

Teaching of Chest Radiology to Medical Students*

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The method of teaching chest roentgenology to medical students at the University of Oregon Medical School is based upon the premise that useful knowledge cannot be attained without practical experience. In a medical school, brilliant teachers cannot serve in lieu of actual patients. Lectures, though superbly organized, illustrated and delivered do not constitute an adequate substitute for realistic clinical experience, no matter the student enthusiasm engendered. X-ray films comprise the bulk of the actual working material of the radiologist insofar as chest disease is concerned.† If for no other reason, this is fortunate for teaching purposes since, unlike the patient, radiographs are easily carried home for study by the student. They can be duplicated at will and each copy retains the reality of the original clinical problem. To fail to exploit this advantage is to do injustice to both the student and academic radiology.

Classes at the University of Oregon Medical School are composed of approximately 70 students. The course in diagnostic radiology is given at the third year level and consists of 33 hour long exercises at weekly intervals. Eleven weeks are devoted to radiology of the chest. In three introductory lectures, an attempt is made to present to the student a three-dimensional concept of the chest as it is reconstructed on two-dimensional x-ray films. Following these lectures, students are assigned cases from the departmental teaching file. These carefully selected cases are prepared *as they might appear awaiting routine dictation in a radiology department or radiologist's office.* A requisition containing clinical data is supplied with the films. In the interest of reality, the clinical information on this requisition varies markedly in quantity and quality. Generally, it is determined by the radiographic findings. Students are allowed to keep the films in their possession for one week. Thereafter and at seven weekly intervals, sessions are held in six small groups, each of which meets with a faculty radiologist. Students, cases and instructors rotate each week. Cases are assigned to the students in bright blue envelopes, a maneuver in the interest of departmental advertising which has to this date not been branded unethical (although the medical school orthopedists are rumored to be

*The Eleventh in a new series of articles prepared under the sponsorship of the Council on Undergraduate Education of the American College of Chest Physicians.

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†Despite widely-held delusions to the contrary, direct radiographs are far superior to fluoroscopy in the ability to detect diseases of the chest. Fluoroscopy's inferiority to radiography in terms of the ability to reveal detail is easily shown. While fluoroscopy is of permanent usefulness only through the fluoroscopist's subjective interpretation of what was noticed, the radiograph shows what was actually there (even though missed). It can be evaluated by many, compared with subsequent or previous films, measured, studied at leisure, reproduced, and even sold for scrap.

considering purple casts). In addition to handing in a written report, students informally present their radiographic findings and interpretations. Lively discussion, at times bordering upon actual battle is customary. That the teaching is retained is evidenced by examinations held at the end of each trimester. These examinations consist of multiple choice questions asked in connection with the projection of slides made from the teaching films used during the trimester.

In addition to the informal conferences, each week a public x-ray quiz is conducted using viewboxes in the medical school library. Members of the class in radiology place their diagnoses in a convenient ballotbox. Interest is favored by knowledge that the student scoring highest on these quizzes will be excused from final examination and given an "A" for the trimester.

The departmental teaching effort is not limited to contact with the medical student during the formal course in radiology. Infiltration tactics are employed in that radiologists assist in the anatomy dissecting room, give short weekly lectures in conjunction with the formal course in pathology and in general are audible contributors to all relevant clinical conferences. These conferences are particularly important in the teaching of diseases of the chest during the fourth year of the curriculum. Often taken for granted, the radiologist's presence at such conferences actually results in a many-fold increase over the number of formal curriculum hours allotted to the Department. An elective in radiology is offered at the fourth year level. Through the reporting of current cases, the elective goes a step farther than the third year home study course in enhancing learning through a realistic practical approach to x-ray diagnosis. In both programs, the faculty-student contact is at the individual level. For teaching programs where this individual relationship is not achieved, it would be equally effective, far cheaper and therefore preferable to replace the faculty with rolls of recording tape.

Although mildly unorthodox, the method of teaching chest radiology at the University of Oregon Medical School appears to be more effective than formalized lecture-demonstrations given in darkened rooms to students rendered drowsy by their inability to see clearly the actual radiographic findings being discussed. Requiring no more preparation than that which is afforded by their every day practice, participation in the conferences of the third year course has proved to be interesting and rewarding to faculty members. It has tended to improve and cement relations between part and full-time faculties. Without imposing a burden, the small conference method gives all members of the volunteer faculty an important role in the teaching of their specialty. The scope of this discussion does not warrant development of this important aspect of medical teaching.

WORLD-WIDE INTEREST IN CHEST CONGRESS IN COLOGNE

Sixty-six countries and territories have indicated that they will send delegates to the Fourth International Congress on Diseases of the Chest to be held in Cologne, Germany, August 19-23, 1956. These countries and territories are as follows:

Alaska
Argentina
Australia
Austria
Belgium
Belgian Congo
Brazil
Bulgaria
Canada
Ceylon
Chile
Colombia
Communist China
Costa Rica
Cuba
Czechoslovakia
Denmark
Ecuador
Egypt
England
Finland
France
Germany
Greece
Haiti
Honduras
Hong Kong
Hungary
India
Iran
Iraq
Ireland
Israel
Italy
Japan
Korea
Lebanon
Liberia
Mexico
Nepal
Netherlands
Pakistan
Panama
Persian Gulf
Peru
Philippines
Poland
Portugal
Portuguese East Africa
Puerto Rico
Republic of China
Romania
Salvador
Scotland
South Africa
Sweden
Spain
Switzerland
Syria
Turkey
Union of Soviet Socialist Republics
United States of America
Uruguay
Venezuela
Viet-Nam
Yugoslavia

More than 200 requests for places on the scientific program have been received from physicians throughout the world. Advance registration for this Congress exceeds that of previous congresses sponsored by the Council on International Affairs of the American College of Chest Physicians. The United States of America will be represented by more than 350 physicians and members of their families.

A large percentage of the physicians attending the Congress will participate in the post-congress tour to Wiesbaden, Heidelberg, Baden Baden, Munich, and Vienna. In Vienna, they will attend the Fifth International Congress of Bronchoesophagology to be held August 31-September 2, 1956.

Herman J. Maersch, M.D.

President

American College of Chest Physicians

1956-1957

DR. HERMAN J. MOERSCH

TAKES OFFICE AS COLLEGE PRESIDENT

Dr. Moersch was born in St. Paul Minnesota March 14, 1895. He received the degree of Bachelor of Science in 1918, the degree of Bachelor of Medicine in 1920, and the degree of Doctor of Medicine in 1921, all from the University of Minnesota. His internship was served in the City and County Hospital in St. Paul from 1920 to 1921. In 1921 he entered the Mayo Foundation as a fellow and was appointed First Assistant in 1923. It was while serving as a fellow in the Mayo Foundation that Dr. Moersch became very much interested in the field of thoracic disease and peroral endoscopy. In 1925, he received the degree of Master of Science in Medicine from the University of Minnesota. At the present time he is Chairman of two clinical sections of medicine at the Mayo Clinic and Professor of Medicine in the Mayo Foundation of the University of Minnesota.

Dr. Moersch has held many important offices in the College, serving as Chairman of the Committee on Scientific Program in 1950, Chairman of the Committee on College Award in 1952, and Chairman of the Council on Research from 1952 to 1955. He has been President of the Minnesota Chapter of the College, as well as a member of the Board of Regents and the Executive Council.

The new President of the College has long been interested in the study of pulmonary and esophageal diseases and has contributed more than 140 articles to the literature concerning problems in these fields as well as numerous chapters in books concerning pulmonary and esophageal problems. He has been especially interested in medical education, and active in the organization of thoracic conferences.

In addition to being a member of the American Medical Association and his County and State medical societies, Dr. Moersch is a Diplomate of the American Board of Internal Medicine and a member of the American College of Physicians, the American and International Bronchoesophagological Associations, the American Association for Thoracic Surgery, the American Trudeau Society, the American Gastroenterologic Association, the Minnesota Trudeau Medical Society, the Minnesota Society of Internal Medicine, the Central Society for Clinical Research, and the Chest Club, and has held office in many of these organizations. He is a member of the Executive Committee of the Minnesota Tuberculosis and Health Association. Dr. Moersch has received honorary membership in the Argentinian, Chilean and Peruvian medical societies. He is a member of Alpha Omega Alpha and Sigma Xi.

Dr. Moersch and his wife, Charline, reside in Rochester, Minnesota. They have two sons: Richard, a fellow in the Mayo Foundation, at present on leave for duty with the U. S. Navy; and Donald, who is a Lieutenant in the Marine Air Force.

College Chapter News

BARCELONA (SPAIN) CHAPTER

The Barcelona Chapter held a scientific meeting on April 14, 1956 at the Instituto Antituberculoso in Barcelona. A panel discussion on tuberculosis was presented in which the following members participated: Drs. M. Gonzalez Ribas, J. Oriol Anguera, A. Castella Escabros, T. Seix Miralta, J. Civil Ingles, E. Bieto Reiman, and J. Bolas Almenar.

EAST INDIA CHAPTER

The annual meeting of the East India Chapter was held at the Great Eastern Hotel, Calcutta, April 6. It was decided that the chapter would present scientific programs every three months, the first to be held on June 30 at the Jadavpur Hospital. The following chapter officers were elected:

President:	K. N. De, Calcutta
1st Vice President:	C. N. Hazarika, Shillong
2nd Vice President:	P. K. Chatterji, Calcutta
Secretary-Treasurer:	P. K. Ghosh, Calcutta

Following the business session, Dr. K. N. De presented a paper on "Intrapleural Isoniazid in the Treatment of Tuberculous Empyema." A discussion period followed, with a summary of the paper and discussion by Dr. P. K. Sen. The meeting closed with a dinner attended by members and guests.

NEW CHAPTER OFFICERS

ALABAMA CHAPTER

President:	Vivian H. Hill, Mobile
Vice President:	Kellie N. Joseph, Birmingham
Secretary-Treasurer:	Joe H. Little, Mobile

ARIZONA CHAPTER

President:	Hans F. Stein, Tucson
Vice President:	D. W. Melick, Phoenix
Secretary-Treasurer:	B. L. Snyder, Phoenix

CALIFORNIA CHAPTER

President:	Marvin S. Harris, Los Angeles
Vice President:	Mortimer A. Benioff, San Francisco
Secretary-Treasurer:	Elmer Rigby, Los Angeles

FLORIDA CHAPTER

President:	Jack Reiss, Coral Gables
Vice President:	Clarence M. Sharp, Jacksonville
Secretary-Treasurer:	M. Eugene Flipse, Miami
Program Chairman:	George L. Baum, Coral Gables

GEORGIA CHAPTER

President:	James C. Metts, Savannah
Vice President:	F. Levering Neely, Atlanta
Secretary-Treasurer:	James Alexander, Savannah
Program Chairman:	William Hopkins, Atlanta

ILLINOIS CHAPTER

President: William M. Lees, Chicago
Vice President: Herman C. Rogers, Mt. Vernon
Secretary-Treasurer: Gordon L. Snider, Chicago (re-elected)

KANSAS CHAPTER

President: Martin J. FitzPatrick, Kansas City
Vice President: Paul H. Wedin, Wichita
Secretary-Treasurer: Robert M. Brooker, Topeka

MISSISSIPPI CHAPTER

President: H. Karl Stauss, Jackson
Vice President: John C. Russel, Cleveland
Secretary-Treasurer: Helen Cannon Bernfield, Jackson (re-elected)

MISSOURI CHAPTER

President: John B. Devine, St. Louis
Vice President: John W. Polk, Springfield
Secretary-Treasurer: David Nafe Kerr, St. Louis (re-elected)

OHIO CHAPTER

President: Harold I. Humphrey, Columbus
Vice President: Virgil A. Plessinger, Cincinnati
Secretary-Treasurer: Francis G. Kravec, Youngstown (re-elected)

OKLAHOMA CHAPTER

President: Will G. Crandall, M.D., Sulphur
Vice President: Robert M. Shepard, Jr., Tulsa
Secretary-Treasurer: George L. Winn, Oklahoma City (re-elected)

PENNSYLVANIA CHAPTER

President: Peter A. Theodos, Philadelphia
Vice President: M. C. Stayer, Harrisburg
Secretary-Treasurer: Ruth M. Wilson, Beaver (re-elected)

TENNESSEE CHAPTER

President: Michael M. Marolla, Memphis
Vice President: Leland M. Johnston, Jackson
Secretary-Treasurer: Perry M. Huggin, Knoxville (re-elected)

TEXAS CHAPTER

President: Walter C. Brown, Corpus Christi
1st Vice President: John A. Wiggins, Fort Worth
2nd Vice President: J. Otis Armstrong, Dallas
Secretary-Treasurer: Lawrence M. Shefts, San Antonio

WISCONSIN CHAPTER

President: Philip Feingold, Wauwatosa
Vice President: George A. Hellmuth, Milwaukee
Secretary-Treasurer: Leon H. Hirsh, Milwaukee (re-elected)

College News Notes

Dr. Charles K. Petter, Waukegan, Illinois, Treasurer of the College, has been appointed Associate Professor of Medicine at the Stritch School of Medicine of Loyola University, Chicago. Dr. Petter has also been appointed Director-at-large and a member of the executive committee for the Illinois Tuberculosis Association.

Dr. P. J. Sparer, Memphis, Tennessee, was elected President of both the Tennessee Psychiatric Association and the district branch of the American Psychiatric Association. Dr. Sparer is Chief of the TB-NP Service at the Veterans Administration Hospital, Memphis.

Dr. Jorma S. Patiala, Helsinki, Finland, was recently appointed Professor of Phthisiology at the University of Helsinki.

Dr. Edward A. Piszczek, Hinsdale, Illinois, is President Elect of the Interprofessional Council and Chairman of the Illinois State Medical Society Committee on Interprofessional Relations.

Drs. Arthur Calix, Decatur, Alabama, **James T. Grimes,** Enterprise, Alabama, and **Duane Carr,** Memphis, Tennessee, presented papers on the scientific program of the annual meeting of the Medical Association of the State of Alabama, held in Birmingham, April 19-20.

Dr. Hunter B. Rogers, Miami, Florida, has been elected President of the Dade County Medical Association.

GOLDEN JUBILEE*

The Golden Jubilee number (January, 1956) of the *British Journal of Tuberculosis and Diseases of the Chest* presents fascinating and authentic accounts of the various phases of the attack on tuberculosis over the past 50 years. Although the microscope and stethoscope had been invented, the tubercle bacillus discovered, tuberculin produced, the x-ray discovered, the bronchoscope invented, and a sanatorium system established before this century began, it was not until after the opening of the 20th century that most of this armamentarium was placed on a practical basis. Only a few numbers of the *British Journal of Tuberculosis* had been issued when safe and practical methods of administering the tuberculin test were reported. Over the 50 years, numerous authors have published their research findings in all phases of tuberculosis work in this journal to inform physicians around the world.

In this Golden Jubilee number, writers of world renown present historical accounts of the fine work that has been done, step by step, over the past 50 years, from meager beginnings to superb accomplishments.

The average number of deaths per annum from 1901 to 1910 was 39,688 in England and Wales. During the 50 years under consideration this dropped to 7,069. Thus, 32,619 persons were living in 1954 who would have been dead had the earlier mortality rate continued.

The *British Journal of Tuberculosis* was the first of its kind. Its editors have been faithful and long serving. The first, Dr. T. N. Kelynack, labored for nearly a quarter of a century. He was succeeded by Dr. L. S. T. Burrell, who then carried on until near his death in 1938. For the next 13 years, Dr. Clifford Hoyle occupied the editorial chair and after retiring from that capacity remained on the board for three more years. For the past six years, the journal has been under the fine editorship of Dr. Philip Ellman. In addition to Editorial Board members from England, Wales, and Scotland, British Dominions are represented by outstanding physicians in diseases of the chest, including Hugh Burke, Canada, Cotter Harvey, Australia, B. A. Dormer, South Africa, F. H. Smirk, assisted by R. F. Wilson, New Zealand.

*Published by Balliere, Tindall and Cox, London.

On reading the fine historical accounts of splendid accomplishments to which this journal has contributed magnanimously, one is impressed with the far-reaching vision of future needs and with discouragement of a spirit of complacency at every turn. Although as its name indicates, this journal deals with all diseases of the chest, from the standpoint of tuberculosis alone, for which it operated so many years, there remains in the citizenry of the British Isles, and in fact, all dominions, as well as every other place in the world, so much residual tuberculosis which will manifest itself clinically as the years and decades pass as to require a tremendous amount of work and publication. In fact, this problem is now so great that it will not be solved until long after this journal celebrates its centenary.

If no new infection occurred after 1956, there are enough persons now harboring tubercle bacilli who will supply such a rich harvest of clinical cases from decade to decade as to command a tremendous force of workers and a huge expenditure of funds.

This fact emphasizes the great importance of perpetuating this journal so that it will play even a greater role in the future than it has in the past in keeping physicians everywhere informed as to the magnitude of the problem and the methods of solution.

Physicians throughout the world will continue to look to the *British Journal of Tuberculosis and Diseases of the Chest* as a fine source of new information.

J. Arthur Myers

BOOK REVIEW

"THE BEHAVIOR OF PULMONARY TUBERCULOUS LESIONS," by E. M. Medlar. Published by the Metropolitan Life Insurance Company, Mount McGregor, Saratoga County, New York, and financed by the Hegeman Memorial Fund. Introduction, by F. H. Ecker and Dr. J. Burns Amberson.

This work, as Dr. Medlar correctly states, is not a text book. It is a monographic compilation of some of the author's work on the pathology, bacteriology and pathogenesis of the disease tuberculosis. There are 10 chapters, a postscript, but no index. With a mere mention of earlier work in the field, he goes into his various studies on animal experimentation, necropsy studies from the Medical Examiner's Office of New York City, medical records from various New York hospitals, and resected specimens from various chest hospitals in the New York area. On these various specimens he has made careful dissection, pathological and bacteriological studies, chiefly pertaining to the disease tuberculosis.

Among many things, he has shown, in spite of the fact that the preponderant majority of tuberculous infections heal, that there is a sizable residue that remain as open lesions, even in minimal disease, for long intervals of time. When a cavity once forms, the tendency is a slow healing even though it may be only a few millimeters in diameter. He has restated clearly the "relay" aspect of the the tuberculous process as it goes from the microscopic focus to a larger, and larger lesion and ultimately to clinical disease. Another important point was the emphasis upon the great and apparently rising prevalence of disease at the present time in people over 40 years of age which he feels is largely re-infection disease and that adults are not exempt from the dangers of infection and disease as was once believed and taught. He has pointed out the predominant role that the neutrophil plays in acute exacerbations of the disease. He shows that bronchial tuberculosis frequently runs a course quite similar to other cavernous forms of the disease and he finally has re-emphasized an old observation that there are what he calls "vulnerable regions" of the lung which are more subject to the development of the disease than any other. He helps to confirm some of the points in this discussion by his animal experimentation.

On the other side of the ledger might be listed some controversial problems. Although Dr. Medlar himself mentioned the fact that some of the work may be "biased," it is clear that there are indeed altogether too few cases under

20 years of age in his studies. A casual reader may also obtain the impression that the earlier work is not as important as some of the recent observations, although Dr. Medlar certainly did not intend to give such an impression. It should be emphasized in passing that the work done by the pioneers, Parrot, Ghon, Aschoff, and many more, has laid the foundation on which all others have built. The term "primary complex" which he uses frequently is one good example and incidentally, it is Ranke's and not Ghon's term expressing the same general principle.

Another deficiency pertains to those dying of clinical tuberculosis. In this group are many types of pathology and many aspects of pathogenesis that would not be found in those dying of sudden or unexpected death or from resected specimens. In this group would be found more true tuberculous bronchiectasis which Dr. Medlar feels is not well founded if not non-existent. Few will go along with him on this. Another objection to the material is that in resected specimens there is not the opportunity to study the lymphatics up to the hilum and beyond. As a result, the studies only are partially informative.

A somewhat distorted impression may be gained from his emphasis upon the all-inclusive role that the neutrophil plays in the tuberculous lesion. In reality the neutrophil is the active agent when the floodgates of resistance are broken and this is seen in most progressive disease. Most healing disease has to do with the longer range type of cell, including the monocyte (macrophage), epithelioid cell and lymphocyte. Some types are fibroplastic throughout like avian tuberculosis in the horse and the "gray-granulation" of Bayle. As to what happens in the earliest hours of the disease, nobody has yet produced every step in every type of disease, including all variations in resistance and in the number, type and virulence of bacilli. The early work of Krause and Willis, Vorwald and others, have presented some of the earlier lesions in animals. What happens in the human being during these early hours and days of infection will perhaps remain obscure for a long time.

There are various other minor issues that may be mentioned in passing. In spite of his failure to find "delayed" progression, nobody knows how long and exactly how many lesions persist over long periods of time and finally develop into disease. Some cases are crystal clear and show a continuous chain of lesions from beginning to end even throughout a lifetime. Others appear to have long lapses of time but nobody knows yet whether the bacilli that caused the lesion were from within or from without. In general, most adult infections after 40 are undoubtedly "exogenous" but the door cannot be closed on the "endogenous" type, especially in younger people. He would have observed more of this type of dissemination had he worked with more children dying of tuberculosis. The same may be said with regard to general and apical localization of lymphohematogenous disease. Such men as Ranke, Redeker, Braeuning, Lydtin, Huebschmann and other Europeans have apparently documented this type of disease fairly well.

The illustrations are unquestionably the most beautiful and prolific of any that have ever been published on the subject. Unfortunately, they are restricted to low magnifications somewhere between two and 15 times diameter. Higher magnifications would have greatly improved the work and made it much more interesting. A few gross photographs would also have been helpful.

The more or less philosophical discussions in what he calls the postscript, are timely. He reiterates the importance of recognizing that re-infection in adults is still a grave threat, that BCG will ever be limited in its usefulness, that the tendency to too much home treatment and the closing of tuberculosis hospitals is definitely premature, and that arguments for resection in pulmonary tuberculosis seem to be quite valid. Finally he asks a series of questions that need to be answered in the future if we are to solve the remaining problems in tuberculosis. In solving these he emphasizes the need for invoking the new skills of biochemistry and bacteriology.

And in all, this work is one of the most valuable on the pathology and pathogenesis of tuberculosis within many years. It is informative, thought-provoking and extremely interesting. No one in the clinical or pathological fields of tuberculosis should be without this monograph.

Henry C. Sweany, M.D.

OBITUARIES

CLETUS J. GOLINVAUX

1896 – 1956

Dr. Cletus J. Golinvaux, a Fellow of the American College of Chest Physicians and former Governor of the College for Michigan, died on February 14, 1956 in Miami Beach, Florida.

Dr. Golinvaux was born in Sanborn, Iowa, May 2, 1896. He received his premedical education at St. Louis University and the degree Doctor of Medicine from that University in 1921.

After many years of practicing internal medicine and chest diseases in Monroe, Michigan, Dr. Golinvaux moved to Miami Beach, Florida five years ago where he was a member of the staff of St. Francis Hospital and the Dade County Medical Association. He was also a member of the American Medical Association and the Bal Harbor Rotary Club.

Surviving are his wife, Mary, four daughters, and two sons.

Arnold S. Anderson, M.D.
Governor

WILLIAM DAVIS TEWKSBURY

1885 – 1955

Dr. William Davis Tewksbury died of a heart condition at his home in Chevy Chase, Maryland, December 28, 1955. Dr. Tewksbury, born in Hutchinson, Kansas, May 7, 1885, was widely known and recognized as an authority on diseases of the chest. He graduated from George Washington University Medical School in 1908 and began practicing medicine in Washington, D. C. that year.

Positions held by Dr. Tewksbury were Clinical Professor of Medicine, George Washington Medical School; Physician in Charge of Health Department, Tuberculosis Clinic and Consultant, and Associate Professor of Medicine at Georgetown Medical School. Dr. Tewksbury was included in the rolls of "Who's Who in America" and was a Fellow of the American Medical Association, American College of Physicians, American College of Chest Physicians, and a member of the Hypocrates Galen Medical Society, Medical Society of the District of Columbia, and was a Director of the Tuberculosis Association of the District of Columbia.

Dr. Tewksbury, who was a pioneer in the use of artificial pneumothorax, visited his office daily until within three weeks of his death. His countless friends and patients who are grieved at his passing nevertheless rejoice in the knowledge that he lived a full and useful life to the end. He is survived by his wife, the former Susan Tidball West, two daughters, Mrs. Jane West Clementson and Mrs. Harry King, and four grandchildren.

E. Raymond Fenton, M.D.

ANNOUNCEMENTS

The Department of Otolaryngology, University of Illinois College of Medicine, will hold its Annual Assembly in Otolaryngology, October 1-7, 1956. The assembly will consist of an intensive series of lectures and panels concerning advancements in otolaryngology, and evening sessions devoted to surgical anatomy of the head and neck and histopathology of the ear, nose and throat. Interested physicians should write to the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Illinois.

The Surgeon General of the U. S. Public Health Service, Dr. Leonard A. Scheele, has announced that qualified physicians and other professional health personnel actively engaged in public health practice and preventive medicine are being encouraged to apply for commissions in the Services' expanding Commissioned Reserve. The Commissioned Reserve is being expanded to increase the nation's readiness to meet the unusual public health demands of national emergencies and the Public Health Service is interested in encouraging greater participation in the program by professional groups. Commissioned Reserve officers will be called for emergency duty primarily to reinforce the staffs of official state and local health agencies and to augment the Public Health Service operating staff. All interested personnel are invited to the Surgeon General, Public Health Service (DP), Washington, 25, D. C., for information.

A new drug which may show promise in the treatment of cancer was disclosed at the recent meeting of the Amercian Chemical Society in Dallas, Texas. Three cooperating groups of researchers combined to report on the new drug, "D.O.N."—a shortened form of its chemical name 6-diazo-5-oxo-norleucine. The associated workers are at the Sloan-Kettering Institute for Cancer Research, the Mellon Institute, Pittsburgh, and the Research Division of Parke, Davis & Company. The new drug is from the class of chemicals known as "amino acids" and according to animal tests, is some thirty times more effective in the control of tumors in mice than is azaserine, an earlier antibiotic. Sloan-Kettering reported that in mice "selected doses of D.O.N. restrained the growth of established tumors and some regression of tumor size occurred. Upon cessation of D.O.N. treatment, the tumor growth resumes." A Parke-Davis spokesman emphasized that no clinical studies had been carried out using the new product. However, laboratory findings indicate some basis for hope, he added.

CALENDAR OF EVENTS

INTERNATIONAL MEETING
Fourth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Cologne, Germany, August 19-23, 1956

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Glenroy N. Pierce, M.D., San Francisco
James Kieran, M.D., Oakland
Robert Stone, M.D., Oakland
William B. Leftwich, M.D., Oakland

MEDICAL SERVICE BUREAU

POSITIONS AVAILABLE

Physician wanted for institutional appointment preferably with experience in the diagnosis and treatment of tuberculosis, although not essential. Must be eligible for or have Oregon license. Higher salary if experienced in chest surgery. Starting salary $7,600 with complete maintenance. Please address all inquiries to Box 287A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Tuberculosis Physician wanted to staff new 200-bed, air-conditioned sanatorium, opening July 1, 1956. Adjacent Medical College of Virginia and its hospital; complete facilities available for chest surgery, surgical and other consultation; out-patient clinics; occupational therapy; rehabilitation; opportunities for teaching and research; eligibility for licensure in Virginia required; all positions covered by social security, state retirement, vacation, and sick-leave.

Medical Director: position open now. Salary range $12,000 to $13,128; five or more years' clinical experience in tuberculosis, four of which served in approved sanatorium and one year in a senior grade; one or more additional years satisfactory experience may be substituted for sanatorium service; Board certification, internal medicine, desirable.

Physician B (3): Salary range, $9,600 to $11,472; two years experience in approved tuberculosis sanatorium or two years in clinic or office practice under supervision of competent chest specialist; two years general practice may be substituted for one year sanatorium or non-sanatorium specialized chest disease experience.

Physician A (1): Salary range $8,400 to $9,168.

Apply to Mack I. Shanholtz, M.D., State Health Commissioner, Department of Health, Richmond 19, Virginia.

Immediate opening for **staff physician** in a 150 bed tuberculosis hospital, equipped to do active medical and surgical therapy. Adequate laboratory facilities. Pulmonary function studies available. Excellent living conditions, which includes a 3 bedroom brick ranch type home. Situated in a metropolitan area consisting of two cities on Indiana side of Ohio River, and Louisville, Kentucky, just across river. Please contact Joseph H. Geyer, M.D., Superintendent, Silvercrest Tuberculosis Hospital, New Albany, Indiana.

Assistant Medical Director wanted for Mineral Springs Sanatorium, Cannon Falls, Minnesota, 100 bed county tuberculosis hospital with active medical, surgical, out-patient, and investigative programs. Salary determined by experience. Furnished home and utilities supplied. Applicant must be male graduate of approved U. S. or Canadian medical school and eligible for Minnesota license. Address: E. V. Bridge, M.D., Superintendent.

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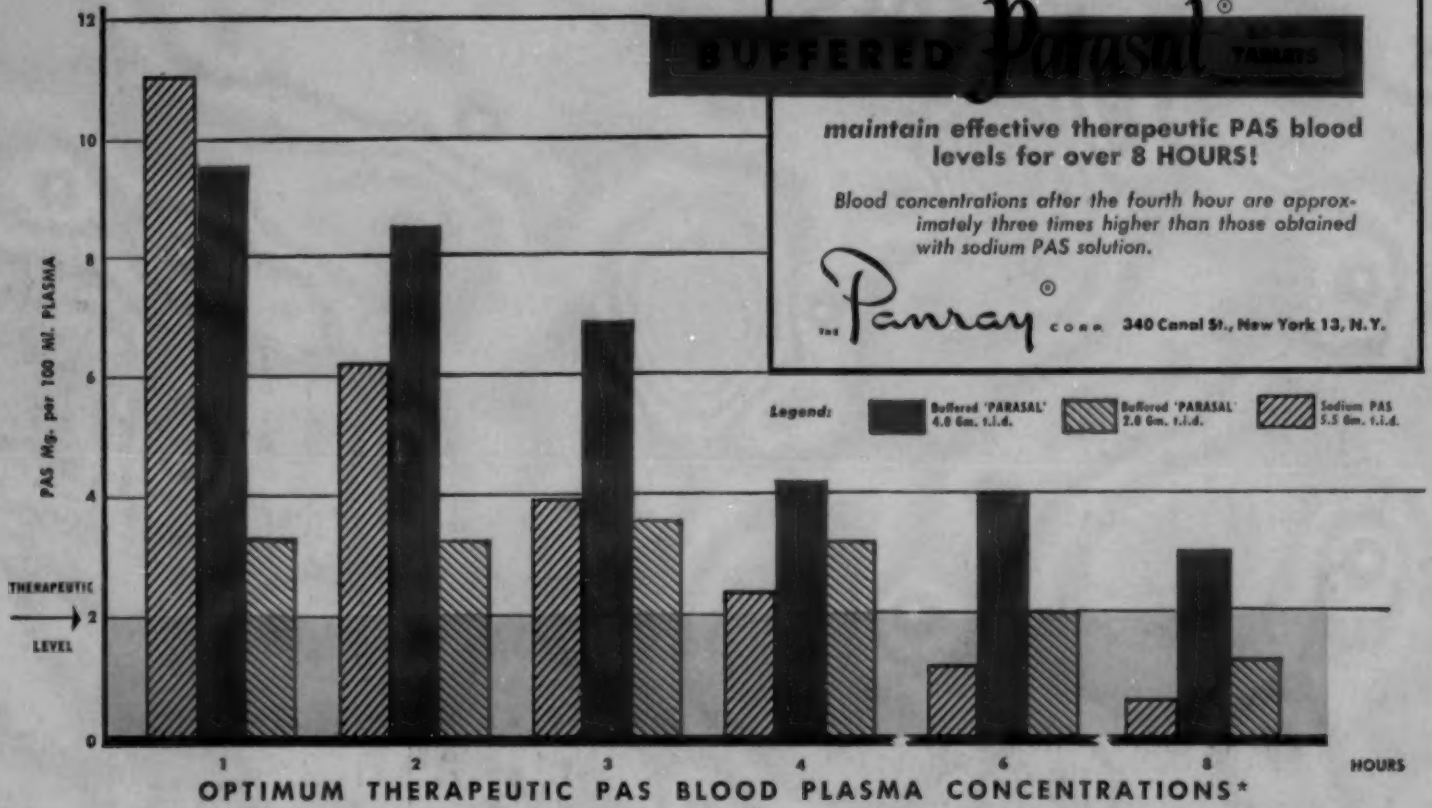

OPTIMUM THERAPEUTIC PAS BLOOD PLASMA CONCENTRATIONS*

Ref.: Deeb, E. N. & Vitagliano, G.R.: A. Rev. Tuber. & Pul. Dis.: 72,543-7 (Oct. '55

*based on multiple dosages, levels determined after 2nd dose of day.